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## EPIDEMIOLOGY OFFICE

Epidemiology Office staff members work with the Associate Director, other EDB Program staff members, other members of the NIA, other investigators at the NIH, Government contractors, the NCHS and other agencies on a variety of analytic, developmental, methodologic, and administrative projects.

Most of the achievements of the Epidemiology Office involved new and continuing analyses of data from established EDB Program projects, including:

### NHANES I Epidemiologic Follow-up Study (NHEFS) -

Work continued at NCHS and WESTAT (the contractor) related to the continuing follow-up of the cohort, including efforts to complete preparation of the 1986 Follow-up of the Elderly data tapes by fall or winter, 1987. The 1987 cycle of telephone interviewing is currently underway. Documentation and data tapes for the initial follow-up ('82-84) are being released to the public this summer. Dr. Cornoni-Huntley continued her efforts to secure funds from sources other than NIA to ensure the full success of the continuing annual/biennial re-followup of this very valuable cohort.

Current plans call for the publication of a book entitled, "Health Status and Well-Being of the Elderly," edited by Drs. Cornoni-Huntley, Huntley, and Feldman, in 1988. That monograph, now nearing completion, will describe the NHANES I/NHEFS and will present information on selected aspects of the health of those participants who were 55 and older at the baseline examination.

Specific analyses of these data were carried out and results presented at scientific meetings and/or submitted for publication related to: osteoarthritis (Mr. Everett, Dr. Cornoni-Huntley, et al); pressure sores (Drs. Guralnik, White, and others); hip fracture (Drs. Farmer, Harris, White, Cornoni-Huntley, and others); and cerebrovascular disease (Ms. Losonczy, Dr. White, Dr. Curb). Other analyses are underway related to: weight (Drs. Cornoni-Huntley, Miles, and others); other anthropometric indicators (Drs. Miles, White, and others); hypertension (Drs. Cornoni-Huntley, LaCroix, and others); angina (Drs. LaCroix, Curb, and others); left ventricular mass and cardiac size (Drs. LaCroix and Cornoni-Huntley); dementia (Drs. White and McWhorter); bowel functioning (Drs. White, Everhart, Roth, and others); pneumonia, septicemia, urinary tract and other severe infectious illnesses (Drs. LaCroix, Lipson, and White); macular degeneration (Drs. Liu and White); and sleep complaints (Dr. White). A special analysis is underway which will use this data set to identify factors which predict longevity among persons who were 65 to 74 years of age at baseline examination, comparing these with factors which were found to predict longevity in a study carried out in the Netherlands (Ms. Deeg, Dr. White, others). In addition to these analyses in which EDB Program staff are directly involved, there are many others that, while they may not involve EDB Program staff as active participants, are nonetheless possible only because of the EDB Program's having established the



NHEFS. The great value of the study and the pivotal role played by Dr. Cornoni-Huntley in its initiation were recognized at the June 1987 meeting of the Society for Epidemiologic Research, by dedication of a half-day session to the NHEFS.

Established Populations for Epidemiologic Studies of the Elderly (EPESE) (Brigham & Women's Hospital N01-AG-0-2107, University of Iowa N01-AG-0-2106, Yale University N01-AG-0-2105, and Duke University N01-AG-4-2110)

The four EPESE continued their data collection during the year, the North Carolina site completing its initial baseline interview, while the other three sites moved toward completion of their sixth annual contact (1 = baseline face-to-face; 2 and 3 = telephone; 4 = repeat face-to-face; 5 and 6 = telephone). Mortality information is now complete for the first 3 years of the study for the three initial sites, and data tapes containing the results of the follow-up face-to-face interview have been received.

Committees for analysis of the mortality, nursing home, and physical functioning EPESE data have been constituted and preliminary data have been generated. [Note: progress toward analysis and publication of these are described under developmental activities and achievements of the Biometry Office]. A committee for analysis of patterns of change in performance on the mental status questionnaire (MSQ), chaired by Dr. White, will begin those analyses this summer. An analysis carried out by Drs. Guralnik, LaCroix and others demonstrated a rise in morbidity in the years prior to death for those ages 65 to 74, 75 to 84, and 85+. Using disability in physical functioning as a measure of morbidity, the rise before death was evident in most sex and age groups from all three centers, with substantially higher rates of disability before death in the oldest strata. These results contrast with previous reports that medicare expenditures in the years prior to death are lower in those aged 85+ than for younger persons. The EPESE analyses also allowed comparisons of rates and levels of disability among participants who died, with their peers of similar age who survived; these comparisons demonstrated more disability in the non-survivors. This difference was greatest among the oldest participants. The finding has implications for the expansion of overall levels of population morbidity as life expectancy continues to increase and more individuals die at older ages.

An analysis of patterns of digitalis use among persons at the three sites is currently being completed (Drs. LaCroix, White, and others), while an analysis of the correlates, predictors, and incidence of angina is just beginning (Drs. LaCroix, Curb, and Guralnik). Dr. Cornoni-Huntley has now finalized plans for a resource data book for the North Carolina Duke EPESE which will be very similar to that already published for the primary sites; publication of this monograph is expected in 1988.

A special ad hoc committee was convened in December 1986, to review the EPESE and make recommendations to the Director. The report of that committee, as a transcript of its executive session, indicated general agreement that the project had been of great value, and that it





continued to possess potential and future research utility. The principal recommendations of this committee focused on an immediate need to define specific hypotheses to be investigated, and on the crucial importance of expanding the data collection to include more objective observations, measurements, and state-of-the-art indicators of physiologic condition and functioning. These general recommendations, again emphasized at the meeting of the EDB Program Ad Hoc Scientific Advisory Committee in June 1987, guide our current planning for these studies.

Senile Dementia: Natural History in a Noninstitutionalized Population  
(Brigham & Women's Hospital/East Boston Neighborhood Health Center  
N01-AG-1-2106)

This study was conceived to define the course of functioning and clinical status over a 3-year interval following the diagnosis of Alzheimer disease in noninstitutionalized persons. Although the initial target date for completion was September 1987, excusable circumstances have delayed completion at least one year. The contract supporting this study differs from other EDB Program contracts in that it does not require the contractor to deliver any data or other materials for possible independent analysis by NIA staff until the study has been completed; prior to that time only interval progress reports are required.

Major results of the study to date include the following findings: (1) the age-specific prevalence curve of total dementia (moderate or severe; probable or very probable) is higher than has been reported in most other studies, rising approximately exponentially to over 50 percent by age 80 to 85, (2) approximately 80 percent of the dementia cases were attributed to Alzheimer disease, and, (3) while no clear-cut predictors except advanced age have yet been identified, lower education seems to be associated with an increased prevalence of dementia. The contractor has submitted two manuscripts for publication, one on patterns and correlates of performance on brief tests of cognitive functioning, and the second describing the initial results of the first cycle of clinical evaluations (including prevalence, correlates, and clinical diagnosis information).

The contractor has now been funded to extend this research through extramural support (NIA grants) for two projects: an Alzheimer Disease Registry (focused heavily on methodologic issues of case ascertainment and classification), and a study of incident dementia, accomplished by utilizing the first and second face-to-face EPESE interviews to identify persons suspected of having become demented, and then carrying out a full-scale dementia evaluation for diagnosis. This series of superbly-conducted investigations will add greatly to our understanding of the epidemiologic aspects of dementia over the next decade or longer.

#### Dementing Illness in the Framingham Heart Study

This study has as its central objective the identification of risk factors influencing the development of Alzheimer disease and vascular dementia. In the course of developing the study, several related



analyses were undertaken by Drs. Farmer, White, Guralnik, and Kittner, including: (1) a description of performance of the subjects on a battery of neuropsychologic tests administered in cycle 14/15 [published], (2) the development of methods for producing an education-standardized and age-unbiased composite score [one paper published, one in preparation], (3) evaluation of the role of hypertension in determining test scores [submitted], (4) an analysis of the association of age with performance on these tests among persons with no major, identified chronic illnesses [presented; revisions in progress], (5) a multivariate analysis of the correlates of cognitive functioning [presented; manuscript in preparation], (6) an analysis of survival and subsequent performance of persons stratified according to performance on the mini-mental state test administered in cycle 17 [presented; additional work in progress], and (7) a study of the interactive influences of cognitive and physical impairments on survival [presented; further work in progress]. An analysis of 5-year outcomes (survival, institutionalization, cognitive and physical functioning) associated with level of performance on this test battery will be initiated by Dr. LaCroix in the near future. An analysis of possible relationships between macular degeneration and the development of Alzheimer disease has also recently begun (Dr. White and Dr. Sperduto, NEI).

Our efforts to identify and classify cases of dementia have taken two simultaneous approaches, one focused on living persons, and the other on study participants who died after the date of their cycle 14/15 examination (i.e., the date of baseline neuropsychologic testing) without having received the standardized examination for dementia. Our plan is to use the "dead case" group in a search for associations (i.e., to generate hypotheses), and to use the "living case" group (i.e., diagnosed with standardized methods) to test these associations and hypotheses. We have now completed detailed reviews of the approximately 600 persons who died, and have identified approximately 80 with dementia, including approximately 43 for whom no cause for the dementia other than Alzheimer disease could be gleaned from clinic and hospital records. These data are currently being transferred from hard copy to computer form, and analyses are expected to be underway within a few weeks. Simultaneously, the contractor has identified approximately 45 cases of Alzheimer disease using standardized examinations, of whom approximately 35 are currently alive.

We are currently working to develop arrangements through the NHLBI contractor that would allow testing of the living cases (and a set of controls) for gene copy number of the beta amyloid protein gene.

Continuation of this project has as its major goals: (1) longitudinal observation of persons previously identified as demented, [a] to confirm the diagnosis, and [b] to develop a better understanding of common patterns of progression; and (2) identifying new dementia cases, [a] to increase the power of other studies, and [b] to define incidence rates more accurately.



#### Other Epidemiology Office achievements:

Dr. Guralnik continued his collaborative efforts with Dr. Schneider toward understanding the relationships between morbidity, disability, and mortality which have occurred this century and which will continue into the next century; their efforts have resulted in a series of presentations and in-press publications. One of these is the lead article for an issue of a gerontologic journal dedicated to the debate over the compression of morbidity, and serves as the focus for commentaries contributed to the issue by a number of notable demographers. Another article published by Guralnik and Schneider dealt with the prospects for extending life expectancy and its implications.

Drs. Guralnik, Schneider, and Ms. Yanagishita will shortly submit for publication a paper on projecting the size of the future elderly population. Their paper reviews methods for such projections and examines the accuracy of past projections using 1937 to 1975 predictions of the 1980 population. Finally, they offer alternatives to recent projections of the population for the 21st century prepared by the Census Bureau.

Ms. Yanagishita and Dr. Guralnik have also submitted a paper which traces age- and disease-specific contributions to mortality improvement in Japan and Sweden from 1972 to 1982, an interval in which Japan surpassed Sweden as the country with the longest life expectancy.

Dr. Miles, working with Mr. Foley and Dr. Guralnik, completed an analysis of National Hospital Discharge Survey data related to the influence of age and other factors on survival following in-hospital cardio-pulmonary resuscitation. (submitted for publication)

Dr. Guralnik completed and will present a series of analyses of morbidity and mortality in later life, based on data from the Alameda County Study.

Ms. Deeg completed a paper describing a measure of longevity she has developed that takes into account sample heterogeneity in sex and age, and that estimates the remaining survival time of survivors (manuscript currently in review).

Ms. Deeg completed a manuscript on the prediction of longevity. In this analysis she compares factors reflecting recent declines in physical and psychological status, with indicators of stable personal characteristics. This analysis was based on data from a Dutch cohort. (submitted)

Ms. Deeg and Dr. Miles examined the relationship between weight change, longevity, and cause of death in a Dutch sample. Declines in weight were found to precede death from most causes. (to be presented)

#### Developmental activities of the Epidemiology Office included:

- development of the content and form of future EPESE interviews/examinations. Dr Guralnik was especially instrumental in the preparation of a proposed protocol for the next in-home assessment that includes several objective examinations and measurements. Dr. LaCroix worked closely with Dr. Cornoni-Huntley and Ms. Campbell





in preparing documents for upcoming EPESE contract extensions and supplements, as well as related to the new OMB clearance packages required for these EPESE activities.

- assistance to the National Center for Health Statistics (NCHS) in its planning of the upcoming (third) National Health and Nutrition Examination Survey (NHANES III). Dr. Guralnik contributed substantially to the final form of the proposed physical disability instruments to be used in the survey. Dr. LaCroix, who was one of the NCHS's key staff in developing the NHANES III prior to joining the EDB Program in May, continued in an active role, strengthening our evolving participation in this national study.
- planning with the NHLBI for possible collaboration in that Institutes's upcoming 4-center project on risk factors for heart disease in the elderly. This project offers special opportunity for research on the correlates, prevalence, incidence, and predictors of dementia. (Dr. Curb and Dr. White)
- preparation for a meeting to be held in Italy in November 1987, to plan an EPESE-like project to study the relatives of EPESE participants who remained in Italy instead of migrating to the U.S. This project represents an opportunity for NIA staff to assist Italian investigators develop studies of possible family related diseases such as hypertension, diabetes, and dementia, and to generate data to be related and compared with information from the East Boston EPESE, the New Haven EPESE, and the East Boston Natural History of Senile Dementia project. (Dr. Cornoni-Huntley and Dr. Guralnik)
- preparation for a joint Israel-NIA meeting on epidemiologic aspects of aging. (Dr. Cornoni-Huntley and Dr. Guralnik)
- cooperation with staff members of the Fels Institute (Yellow Springs, Ohio) and the Washington Hospital Center to develop, standardize, and employ anthropometric indicators of body composition in the assessment of nutrition and general health in older persons, and to develop improved means for estimating total body fat from conventional measurements. Dr. Miles emerged as the key staff person in the EDB Program's developing interests in these areas. (Dr. Miles, Dr. White, Ms. Deeg, Ms. Losonczy and Dr. Cornoni-Huntley)
- contact was established with investigators from several other nations (including Canada, New Zealand, Japan, and the U.K.) interested in developing EPESE-like studies which might yield comparable information on the health of their older populations. (Dr. Cornoni-Huntley)
- collaboration in analysis of a longitudinal study of older persons in Florida--the Dunedin Project. Dr. Miles is currently collaborating with Dunedin investigators in the analysis of their serial anthropometric data.



- proposal of a project for possible AID funding. The proposal called for coordinated epidemiologic surveys in 2 to 4 developing nations in the Asia/Pacific region. The proposed studies would be focused on physical and cognitive functioning, hearing and vision. As envisioned, the foreign surveys would be established and managed by a contract-funded coordinating center, probably located in Hawaii, with scientific oversight provided by a steering committee including the NIA project officer, and representatives from AID and WHO. In addition to the surveys in the collaborating nations, parallel surveys would be conducted by the coordinating center in subpopulations of corresponding ethnicities migrant to the U.S. from the collaborating nations. (Dr. White and Dr. Curb)
- possible cooperation with the NHLBI in reexamination of the approximately 5,500 surviving participants in the Honolulu Heart Study. The main focus of the proposed NIA study would be on dementia and other aspects of central nervous system (CNS) aging. (Dr. White and Dr. Curb)
- development of the "compression of morbidity" hypothesis. One of the most important implications of the Fries hypothesis (that this century's "rectangularization" of survival curves, in conjunction with postponement of morbidity, will lead to a "compression of morbidity") is that age-specific prevalence ratios for morbidity indicators (such as impairments and disabilities due to chronic disease) should be decreasing. Two essentially identical national surveys, conducted during the 1960's and 70's by Dr. Ethel Shanas for the Social Security Administration, could be used to test this hypothesis. Dr. Guralnik and Dr. Miles have discussed this with Dr. Shanas; she declined to be an active collaborator but graciously provided the data tapes for their analysis, now just beginning.
- further development of opportunity for defined, cooperative analyses of data from the Systolic Hypertension in the Elderly Project (SHEP). Although the NIA has been a major contributor of funds for SHEP, the NHLBI has taken the major role in management and has received the lion's share of recognition. Drs. Page and Sluss-Radebaugh (NIA extramural scientists) have represented the NIA in recent years and have recognized the potential of the SHEP data for many aspects of research on aging. NIA's access to these data is now further facilitated by Dr. Curb's prior position of leadership as a SHEP principal investigator and his continuing participation on SHEP committees. Further development of this opportunity for defined, cooperative analyses is anticipated. (Dr. Curb)

#### Research Highlights, FY 1987

- Research on the predictors of hip fracture in white women suggests that both low skinfold thickness and low calculated arm muscle area are independently associated with an increased risk for hip fracture, and that together, these measures are better predictors of fracture than either weight or relative weight alone. Because these indicators of body composition vary systematically with sex, race, and bone density, the finding implies that body composition may be the unifying factor



underlying risk variation by sex and race, and suggests that such simple measurements may replace or complement other more costly indicators of fracture risk.

- Research on the rates and predictors of stroke suggest that the lifetime risk for cerebrovascular disease probably exceeds 25 percent, and confirms systolic blood pressure and elevated hemoglobin levels as important risk factors. While black males were found to be at increased risk for stroke compared to white males, race differences were not significant in women. Diabetes was found to be an important risk factor for stroke in women but not in men. This analysis did not confirm previous reports suggesting a protective effect for high dietary potassium intake, or for an increased risk associated with obesity, cigarette smoking, alcohol, or dietary fat intake.
- Preliminary analysis of data from a national study suggests that risks for the development of dementia are substantially increased in the presence of diabetes, and that inactivity and infrequent bowel movements may be early signs of incipient dementia.
- Data from an Italian-American community in East Boston suggest that rates for dementia among community-dwelling elderly may be greater than previously estimated, that 75 to 80 percent of the dementia may be due to Alzheimer disease, and that lower education may be associated with a modest increase in the occurrence of dementia.
- A study on the predictors of pressure sores identified no strong constitutional or "exposure" risk factors, thereby supporting the accepted view that the risk of a decubitus ulcer is more related to the nature of the person's reason for being immobilized and the care he receives during the course of the illness.
- A study on survival following in-hospital cardiopulmonary resuscitation confirmed the expected decreasing survival rate with increasing age. Survival rates were lowest in older, married males.
- An improved method was developed for demographic projections. The method was used to generate projections of older population to the 21st century, yielding somewhat different figures than those released by the U.S. Census Bureau.
- An analysis of available demographic data demonstrated that, between 1972 and 1982, Japan surpassed Sweden as the country with the longest life expectancy. While cerebrovascular disease mortality rates remained lower in Sweden over the interval, the rapid gain made in Japan relative to Sweden for this cause of death was a prime factor in the change. Japan's improving life expectancy was largely related to declining mortality rates among persons aged 55 and older.





DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 02010 09 EDBP

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

NHANES I EPIDEMIOLOGIC FOLLOWUP STUDY (NHEFS)

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Joan Cornoni-Huntley, Ph.D., M.P.H.  
Deputy Associate Director, EDBP, NIA

COOPERATING UNITS (if any)

National Center for Health Statistics, Division of Analysis; NCI; NHLBI;  
NIADDK; NIMH; NIAAA; NIAID; AND NINCDS.

LAB/BRANCH

Epidemiology Office

SECTION

Epidemiology, Demography, and Biometry Program

INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:

.40

PROFESSIONAL:

.20

OTHER:

.20

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unredacted type. Do not exceed the space provided.)

The purpose of this project is to design and complete a follow-up of persons examined in the NHANES I to study how factors previously measured relate to the health conditions that have developed since the survey. The three major areas for prediction of outcome are 1) risk factors for chronic disease; 2) nutrition; and 3) health care utilization. The survey has a household interview including self-reporting of health conditions, dietary history and behavioral and social status plus some physical measurements such as blood pressure, height, and weight. Death certificates and hospitalization records will be acquired for all reported events. Work continued at NCHS and WESTAT (the contractor) related to the continuing follow-up of the cohort, including efforts to complete preparation of the 1986 Follow-up of the Elderly data tapes by fall or winter, 1987. The 1987 cycle of telephone interviewing is currently underway. Documentation and data tapes for the initial follow-up ('82-84) are being released to the public. Efforts continue to secure funds from sources other than NIA to ensure the full success other than NIA to ensure the full success of the continuing annual/biennial follow-up of this valuable cohort.

Current plans call for the publication of a book entitled, "Health Status and Well-Being of the Elderly," edited by Drs. Cornoni-Huntley, Huntley, and Feldman, in 1988. The monograph, now nearing completion, will describe the NHANES I/NHEFS and will present information on selected aspects of the health of those participants who were 55 and older at the baseline examination.

Costa, P., Zonderman, A., McCrae, P. Cornoni-Huntley, J., Locke, B., Barbano, HE. Longitudinal analyses of psychological well-being in a national sample: stability of mean levels. J of Gerontol. 41(1):50-55, 1987.

EDBP-12



CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL (N01-AG-0-2107)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$515,464

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substudies on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies. High priority short term studies will be encouraged.

Proposed Course: A 6-month extension and the addition of a third in-person interview and brief physical examination is proposed in the sixth year of follow-up.



## CONTRACT

Name and Number: UNIVERSITY OF IOWA (NO1-AG-0-2106)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$482,500

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substudies on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Major Findings: A total of 9,955 prescription or nonprescription drugs were reported by the respondents. The overall mean number of drugs per respondent was 2.87, while 12 percent of all respondents were not taking any drugs. Mean prescription and overall drug use increased significantly with increasing age ( $P < .001$ ), while mean nonprescription drug use was relatively constant across age groups. Significantly more women were prescription and nonprescription drug users. Directions for scheduled daily dosing accounted for 75 percent of all directions. The majority of prescription and nonprescription drugs had been taken on the previous day. General practitioners accounted for more prescription drugs (39.7%) than any other medical specialty. The most frequently stated purpose was cardiovascular for prescription drugs and musculoskeletal nonprescription drugs. The most frequent prescription drug therapeutic categories were cardiovascular (54.7%), central nervous system (CNS) agents (11.4%), and analgesics (9.4%). For nonprescription drugs, the three most frequent therapeutic categories were analgesics (39.6%), vitamins and minerals (32.9%), and laxatives (14.1%).

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge, it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: A 6-month extension and the addition of a third in-person interview and brief physical examination is proposed in the sixth year of follow-up.

Publications: Helling, D.K., Lemke, J.H., Semla, T.P., Wallace, R.B., Lipson, D.P., Cornoni-Huntley, J.: Medication characteristic use in the elderly: The Iowa 65+ rural health study. J Am Geriatr Soc. 35:4-12, 1987.





# CONTRACT

Name and Number: YALE UNIVERSITY (N01-AG-0-2105)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESE)

Date Contract Initiated: June 30, 1980

Current Annual Level: \$596,009

Objectives: The purpose of this project is to conduct epidemiologic investigations in a community to develop new knowledge concerning the medical and social factors in health and diseases of the aged. Within the major prospective study are substudies on problems of pain, vision, hearing, sleep, drug use, constipation, social support and other pertinent areas.

Methods Employed: The project shall include cross-sectional and prospective studies in a carefully defined and accessible population using standard field and analytical techniques. Yearly surveillance of the population will be included.

Significance to Biomedical Research: The population over age 65 has been steadily increasing both in relative and absolute numbers. With this increase has come an awareness of a variety of health and social problems which are creating problems for our social and physical environment. To provide new knowledge it is important to have studies representing existing conditions in a community population. Within obvious logistical constraints populations will be available to the NIA scientific community for specific studies.

Proposed Course: A 6-month extension and the addition of a third in-person interview and brief physical examination is proposed in the sixth year of follow-up.



## CONTRACT

Name and Number: DUKE UNIVERSITY MEDICAL CENTER (NO1-AG-4-2110)

Title: Established Populations for Epidemiologic Studies of the Elderly (EPESI)

Date Contract Initiated: September 30, 1984

Current Annual Level: - 0 -

Objectives: Duke University Medical Center is studying an elderly population of at least 4,500 noninstitutionalized persons, 65 years of age or older, and of which at least 50 percent is black and approximately 30 percent to 40 percent is white. The Population is stable with a wide range of socioeconomic status in both black and white groups. The influence of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the study population will be investigated.

Methods Employed: Descriptive and analytical epidemiologic studies of existing problems and surveillance of newly developing problems all with an emphasis upon future intervention and prevention will be conducted. Investigators will conduct cross-sectional and prospective studies as well as more detailed problem-related studies in a carefully defined and accessible population using standard field and analytical techniques. During the first year the population was defined ecologically in terms of social, political, and demographic characteristics; and working relationships were established with the public and professional groups within this population.

Major Findings: Instruments were developed and pretested, specific research goals were defined, and coordination with the three existing population studies developed.

Significance to Biomedical Research: The NIA is at present funding three population studies of the elderly to determine the influences of social, environmental, behavioral, and economic forces on the mortality, morbidity, and utilization of health services in the elderly. These studies, however, are not fully representative of the U.S. elderly, specifically, they do not include a significant proportion of blacks. It is well known that distributions of certain risk factors and diseases differ between U.S. blacks and other racial groups. Therefore, the purpose of this contract is to conduct epidemiologic investigations in an elderly population of which at least 50 percent is black in order to develop new knowledge concerning the medical and social factors in health and diseases of the aging black population.

Proposed Course: A baseline survey of the population is being conducted at present to obtain baseline data and an estimate of the participation rate for the specific problem-related studies. The 2nd through the 6th years shall be devoted to continual surveillance of the population, analysis of data, and development and completion of problem-related studies. A final household interview shall be conducted in the 5th year.



## CONTRACT

Name and Number: PETER BENT BRIGHAM HOSPITAL/  
EAST BOSTON NEIGHBORHOOD HEALTH CENTER (NO1-AG-1-2106)

Title: Senile Dementia: Natural History in a Noninstitutionalized Population

Date Contract Initiated: June 16, 1981

Current Annual Level: \$133,271 .

Objectives: The objective of this study is to describe the course of general health and cognitive decline in a group of SDAT victims and controls.

Methods Employed: Persons suspected of being demented because of performance on a screening examination will receive a neurological and neuropsychological evaluation. SDAT cases and a number of matched controls will then be reexamined at yearly intervals over a period of approximately 3 years; thereafter the cases and controls will be followed as defined by their participation in another EDBP study (EPESE)--for death, hospitalization, and institutionalization end points.

Major Findings: First two waves of clinical evaluations completed, third wave begins; initial analyses from the baseline evaluation complete, data presented at meetings and in papers submitted and in preparation; results indicate an age-specific prevalence among East Boston elderly more than double usual community estimates, with a substantially higher proportion attributed to Alzheimer disease than usually expected, very few cases of dementia attributable to "reversible" causes, very few cases previously recognized as suffering from dementia, and with an unexpectedly strong relationship between selected motor signs and cognitive impairment.

Significance to Biomedical Research/Justification: This study will provide a better understanding of the prognosis and clinical course of SDAT.

Proposed Course: This study was conceived to define the course of functioning and clinical status over 3-year interval following the diagnosis of Alzheimer disease in noninstitutionalized persons. Although the initial target date for completion was September 1987, excusable circumstances have delayed completion at least one year.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 04003 06 EDBP

## PERIOD COVERED

October 1, 1986, to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Dementing illness in the Framingham Heart Study

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Lon R. White, M.D., M.P.H.

Chief, Epidemiology Office, EDBP, NIA

Jack M. Guralnik, M.D., Ph.D.

Senior Staff Fellow, Epidemiology Office, EDBP, NIA

Andrea Z. LaCroix, Ph.D.

Epidemiologist, Epidemiology Office, EDBP, NIA

## COOPERATING UNITS (if any)

NHLBI

## LAB/BRANCH

Epidemiology Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

0.5

## PROFESSIONAL:

0.5

## OTHER:

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Demented subjects are identified by a 2-phase evaluation: administration of the screening test as part of the regular biennial examination, coupled with neurological and neuropsychological evaluations of participants who fail the screening test. A second group of dementia cases will be identified from among recently deceased study participants based on: (a) poor performance on neuropsychological tests administered approximately 5 years ago, (b) review of medical records, and (c) telephone interviews with a surviving family member.

Continuation of this project has as its major goals: (1) longitudinal observation of persons previously identified as demented, [a] to confirm the diagnosis, and [b] to develop a better understanding of common patterns of progression; and (2) identifying new dementia cases, [a] to increase the power of other studies, and [b] to define incidence rates more accurately.

Publications: Farmer, M.E., White, L.R., Kittner, S.J., Kaplan, E., Moes, E., McNamara, P., Walls, M., Wolf, P.A., Feinleib, M. Neuropsychological test performance in Framingham: A descriptive study. Psychological Reports. 70:1023-1024, 1987.





## DEMOGRAPHY AND ECONOMICS OFFICE

A paper has been written and entitled, "The Economic Cost of Senile Dementia in the United States, 1985." The authors are Drs. Lien-fu Huang, William S. Cartwright, and Teh-wei Hu. This paper attempts to estimate various costs associated with the care of senile dementia based on available secondary data. The total direct cost of senile dementia is \$13.26 billion, which includes \$6.36 billion of medical care costs, \$2.56 billion of nursing home care costs, and \$4.34 billion of social agency services costs. The indirect cost for community home care alone is \$31.46 billion, more than twice the total direct cost. The cost of premature death and loss of productivity due to senile dementia are even higher, about \$43.17 billion. Although most of the indirect costs were imputed from the value of housekeeping or productivity loss, the magnitude of indirect costs reflected the serious consequences and burden on society's resources of this disease. The paper is submitted for review.

A paper entitled, "Demand for Health Insurance by the Elderly: A Microsimulation Model" (authors Huang, Cartwright, and Hu) was presented at the Western Economics Conference, July 7-11, 1987. An important national issue is the appropriate mix of the public and private sector in the provision of health insurance to the elderly. Hence, it is important to understand the demand for "Medigap" insurance policies and the interaction between Medicare and Medigap policies. A theoretical model of health insurance demand is developed which corrects some problems in the development of former applications. The model examines the effect of the individual's health status, public and private insurance subsidies, the mix of third party and out-of-pocket payment and the utilization of health care services. Loading costs play an important role and are defined as the difference between the total premiums paid out in benefits by the insurance firm and those retained for administrative costs, profits, and reserves. Large loading costs drive up the price of insurance and have a large hypothetical depressing impact on the insurance demand by the elderly who are not receiving subsidies through employer contributions or tax benefits on their premiums.

A research paper entitled, "Health and Retirement: A Follow-up Study" has been completed by Drs. Cartwright and Cornoni-Huntley. An earlier version was presented at the meetings of the Gerontological Society of America in November 1986. This paper estimates the impact of heart disease, arthritis, and respiratory disease on the work outcomes of a cohort of males who were initially working at the time of the NHANES I study and who were alive and interviewed in the NHANES Epidemiologic Follow-up Study (NHEFS). The presence of self-assessed arthritis and respiratory diseases were significantly and negatively associated with participation in the labor market. This has been submitted for review.

ICF, Incorporated (Contract N01-AG-3-2117) submitted a draft final report entitled, "A Macroeconomic-Demographic Model of Health Care and Consumer Expenditures." This report contributes to NIA's work in the area of the macroeconomics of aging. The study develops an econometric model of total consumer expenditures (health care, food, consumer goods, capital services, consumer services) and then disaggregates health care (hospital, physician, dental, other professional services, drugs, and appliances). The study



details a review of the literature, data base development, estimation results, updating the population model, a discrete/continuous translog model of health care demand, and demographic and health care expenditures of the institutional population from 1950 to 1980.

ICF, Incorporated submitted a draft final report on Task 6 of contract N01-AG-2-2138 and final report on Task 1 of contract N01-AG-3-2117. This details the simulation model for projecting consumer and health care spending behavior of the noninstitutional population. Projections are presented of total consumer expenditures and health care, food, consumer goods, capital services, and consumer services. Annual projections are made of expenditures for hospitals, physicians, dental services, other professional services, drugs, and appliances. Demographic projections of the population by age, sex, region, urban or rural, race, income, and those with health insurance and without health insurance. Projections are also made of the source of payment (out-of-pocket, private insurance, Medicare, Medicaid, etc.) by year and demographic group. Projections are presented for households under 65, households aged 65 to 74, and households 75 and older. This work will be finished July 30, 1987. The analysis of health and the demographics of aging will be finished by September 30, 1987. "Updating and revising the Macroeconomic-Demographic Model" (MDM) (Contract N01-AG-4-2107) continues on the new time schedule. ICF, Incorporated transmitted a draft report on the Labor and Macroeconomic Growth Models entitled, "Revision of the Macroeconomic Growth Model and Labor Market Model of the NIA Macroeconomic-Demographic Model, June 30, 1987." New aspects to the growth model are:

1. A new intertemporal allocation procedure for consumption;
2. Introduction of "a multiple shooting" to solve the model;
3. New labor demand equations; and
4. Revision of the government expenditures and the rest of the world sectors.

The revision of the data base are up to 1985, the last National Income and Products Accounts revision and rebenchmark. The new models shall be re-incorporated into the NIA MDM.

"Household Formation and Housing" (Contract N01-AG-5-2106) has developed a protocol for "A Discrete/Continuous Translog Model of Housing Demand." In this approach, households first decide the tenure or type of housing they wish to consume. Contingent on this choice, the second stage of the decision process is the determination of the quantity of housing services. The expected demands of individuals are obtained by summing across the conditional demands in all tenures in which the weights are the probabilities of choosing a specified housing alternative. Household formation will be developed from a demographic model of the long-term trends. In-kind transfers for food, housing, and medical care will be incorporated into the econometric model.



The EPESE Hospitalization Committee is making progress. First, the outcome of the hospitalization event and the length of stay are being analyzed. This is facilitated by the matching of Medicare Part A administrative records on the sample in the East Boston, New Haven, and Iowa sites. New Haven and Iowa are waiting for a new round of matches from Health Care Financing Administration (HCFA). East Boston is in the best shape because of matching through Massachusetts Blue Cross and Blue Shield. In addition, all sites have submitted tapes to HCFA to match Medicare Part B administrative records. Work now focuses on cleaning up the Medicare Part A data.

Dr. Cartwright collaborated with other members of the EDB Program on a chapter entitled, "Geriatric Epidemiology," which was published in the Annual Review of Gerontology and Geriatrics, Volume 6, 1986. Dr. Cartwright also collaborated on the chapter entitled, "Development of the Epidemiology, Demography, and Biometry Program at the National Institute on Aging," which will soon be published by Springer Publishing Company.

In training, we have had three successes. First, Dr. Robert Friedland who received his Ph.D. from George Washington University and conducted part of his thesis studies at NIA is conducting research on long-term care for the Employee Benefit Research Institute. Assistant Professor Alfred Drummond, Goucher College, has completed a draft of his thesis (The Life Cycle Model and Precautionary Savings) and will be defending it in September of this year. Robert J. Buchanan, a Robert Wood Johnson Foundation Fellow at the NIA recently published his book entitled "Medicaid Cost Containment" which he worked on while in residence at NIA. There is no economic training being conducted at this time.

#### Research Highlights. FY 1987

- The health care costs of the institutionalized population differ significantly from the noninstitutionalized population because of advanced age, disability, or infirmity. Medical and custodial care are both required. Data on the size and composition of the institutionalized population are incomplete and often inconsistent. Estimates were made of custodial care and direct health care expenditures of the institutionalized population from 1950 to 1980. Estimates were derived from The National Health Accounts, an HHS study, and the National Medical Care Utilization and Expenditure Survey (NMCUES). U.S. Census Bureau data is used for population counts of the institutionalized by age, sex, and race. For personal health care expenditures Table 1 depicts a total of \$35.8 billion for the 2,025.8 (thousands) individuals in institutions (excluding correctional facilities).





Table 1: Estimate of Personal Health Care Expenditure 1980;  
Institutionalized Population (Billions of dollars).

<u>Type of Service</u>	<u>Total Payment</u>
Hospital	\$ 12.9
Physician	1.3
Dental	.3
Other Professional	.3
Drugs	.3
Appliances	.1
Other Health	<u>.1</u>
Subtotal	\$ 15.3
Nursing Home Care	\$ <u>20.5</u>
Total	\$ 35.8

(Final Report A Macroeconomic-Demographic Model of Health Care and Consumer Expenditures April 30, 1987, Contract N01-AG-22138.)

- One of the special problems facing the elderly is the financing of their demand for health services. While most elderly have Medicare coverage; 64 percent will purchase supplemental private insurance, 13 percent will receive Medicaid coverage, and 23 percent will have only Medicare coverage. Using simulation modeling, the effect of subsidizing insurance premium for Medigap supplemental insurance is examined. The optimal level of coverage, as represented by the coinsurance rate, varies considerably depending on attitudes toward risk, the price elasticity of medical care demand, and the loading costs. Insurance premium subsidy by either the public or private sector will increase the demand for private Medigap supplemental insurance and will reduce the coinsurance rate. The high loading costs typically faced by the elderly has a rather large depressing effect on the optimal level of coinsurance. The simulation model implies an insurance coverage on total medical care services of 74 percent (or a 26 percent average coinsurance rate). Care must be taken in interpreting the results of the simulation model, because they are hypothetical until further empirical verification (Contract N01-AG-5-2107).



# CONTRACT

Name and Number: ICF, Incorporated (NO1-AG-4-2107)

Title: Updating and Revising the Macroeconomic-Demographic Model

Date Contract Initiated: September 26, 1984

Current Annual Level: \$253,046

**Objectives:** The objective is to update and revise the MDM. This will involve both re-estimation and other revisions to the equations and structure of the model in order to update the model from newly available data and from institutional changes in Federal programs. The end result will be an updated new base case for the computer simulation model that can be used for analysis of policy change and population aging. This work shall be consistent with the ongoing modeling.

**Methods Employed:** The NIA MDM is a complex computer simulation model. It consists of a large FORTRAN program that is over 7,000 lines long and has 43 sub-routines and a main program. The equations that make up this computer simulation model come from mathematical relations of the actuarial and the demographic sciences, as well as behavioral relations from economic science. The behavioral relations are statistically based equations that are estimated from underlying data bases. The equations are conceptually grouped into various models depicting key aspects of the economy. These models are the Population Model, the Macroeconomic Growth Model, the Labor Market Model, the Social Security Model, the Private and Public Employee Models, the Supplemental Security Income Model, and the Medicare Models. There are ongoing contracts to develop health and consumption expenditures modeling that shall add equations to the computer simulation model.

**Significance to Biomedical Research:** The demographic structure of the U.S. population is aging. This has profound implications for the nation as an increasing number of elderly survive into older and older ages. The NIA MDM projects a 150 percent increase in those 65 and older from 1980 to 2050. This will affect Federal programs for both health and income security. In particular, health information shall be enhanced through this updating process so that critical aspects of population aging and health policy may be examined with more immediate policy relevance. Further, there will be immediate near term requirements for analyses of the social security system and civil service retirement system.

**Proposed Course:** A new base population and adjustment factors derived from the 1980 Census of the U.S. population will be incorporated. An alternative base population shall be developed that is consistent with the Social Security projections. A new set of projections will be constructed for the base case consistent with Census and Social Security projections.



## CONTRACT

Name and Number: ICF, Incorporated (N01-AG-5-2106)

Title: Household Formation, Housing and the Aging Population

Date Contract Initiated: June 30, 1985

Total Cost of Contract: \$252,180

Objectives: The purpose of this contract is to investigate household formation and the interactions with the aging United States population and the economy.

Methods Employed: This work shall involve analysis of appropriate data bases and econometric modeling. The NIA Macroeconomic-Demographic Model (MDM) shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM is a key task in this project. Another particularly important aspect is the interaction of housing and household formation. Because housing and household formation are so closely related, a housing model will be constructed and integrated with the NIA MDM. The resultant household formation model and the housing model will permit an examination of the implications of an aging population in the United States. The contractor is required to acquire existing data bases for utilization in the modeling.

Significance to Biomedical Research: The NIA supports the MDM which permits study of the relationship between the economic status of the elderly and the national economy. As population aging continues through the 20th century and into the 21st century, the complicated mechanisms of economic dependency and related health effects must be continually studied. For example, the health and welfare of the elderly will be affected both by the evolution of the economy and the income security system. The current NIA model has previously focused on retirement income issues and is now being developed in the area of a detailed health expenditures model.

Proposed Course: This work shall involve analysis of appropriate data bases and econometric modeling. The NIA MDM shall be augmented by the resulting behavioral relations developed in the analysis. Thus, a method of integrating household formation with the MDM shall be accomplished under this contract. Additionally, a housing model shall be constructed and integrated with the MDM. The resultant household formation model and the housing model shall permit an examination of the implications of an aging population in the United States.



## CONTRACT

Name and Number: Applied Systems Inst., Inc. (N01-AG-5-2107)

Title: Microeconomic Analysis of Aging, Health Status and Conditions, and Health Expenditures

Date Contract Initiated: September 23, 1985

Total Cost of Contract: \$236,514

Objectives: The specific objective of this contract is to focus on the microeconomic analysis of aging and health, i.e., the health status and condition of the elderly and their health care demand. This work involves reviewing the relevant literature on aging and health economics, estimating the effect of health status and health conditions, as well as other independent variables on health utilization, and analyzing the results with regard to the elderly population and their health needs.

Methods Employed: The work performed under this contract is of a scientific and technical nature and directed to understanding health expenditures in the elderly population. An important aspect of health expenditures is understanding the role of health status and health conditions in the demand for health care by the elderly. Therefore, a careful development of the joint demand for insurance and health care must be done along with consideration of such aspects as Medicare, Medicaid, and Private Supplemental Insurance. The simulation model will be developed to explore the various aspects of health expenditures with respect to prices, income, private insurance programs, Medicaid, and demographic groups. In addition, an empirical model of elderly health expenditures will be developed and estimated with data available from cross-sectional surveys. Thus, analysis will be done on publicly available data resources and no primary collection of household survey data will be made.

Majors Findings: Using simulation modeling, the effect of subsidizing insurance premium for Medigap supplemental insurance is examined. The optimal level of coverage, as represented by the coinsurance rate, varies considerably depending on attitudes toward risk, the price elasticity of medical care demand, and the loading costs. Insurance premium subsidy by either the public or private sector will increase the demand for private Medigap supplemental insurance and will reduce the coinsurance rate. The high loading costs typically faced by the elderly have a rather large depressing effect on the optimal level of coinsurance. The simulation model implies an insurance coverage on total medical care services of 74 percent (or a 26 percent average coinsurance rate). Care must be taken in interpreting the results of the simulation model, because they are hypothetical until further empirical verification.

Significance to Biomedical Research: The NIA/EDB Program is already supporting the development of a health expenditures model for the NIA Macroeconomic-Demographic Model of the U.S. economy. This work emphasizes a population aging focus within a macroeconomic framework. The current work focuses on microeconomic considerations in the health market for the elderly.

Proposed Course: This contract terminates November 1987.





## BIOMETRY OFFICE

The FY 1987 activities of the Biometry Office have continued from those conducted in FY 1986, with an increasing emphasis on data management and data analysis for a variety of studies maintained by the EDB Program. Staff members have been heavily involved in numerous projects related to the Established Populations for Epidemiologic Studies of the Elderly (EPESE), the NHANES Epidemiologic Follow-up Study (NHEFS), and with the recent completion of fieldwork and arrival of data tapes, the Survey of the Last Days of Life. Our liaison and consultative activities with other programs, institutes, and agencies has continued, primarily with the National Center for Health Statistics (NCHS) and the other NIA programs and NIH institutes involved in the NHEFS. Further, some methodological studies have moved further toward completion and others into the planning and development stages. An interagency agreement with NCHS has been executed to complete the NIA support for the National Mortality Followback Survey, and another agreement written for support of an NCHS project for development of software for rigorous statistical analysis of complex sample survey data.

The EPESE Resource Data Book has been completed, with 7,000 hard cover copies printed. Work will begin soon on the supplement to this book containing baseline data from the fourth center located at Duke University. The data management and programming staff has already begun the planning for the supplement in anticipation of early arrival of the data tape from the contractor. Plans call for an increased level of automation in the production of this publication, using camera-ready personal computer graphics produced in-house and desktop publishing of the text as well as computer-generated and automatically-typeset tables. Not only will this system be far less costly, but the 3-week period previously required to produce tapes and receive galleys from the Government Printing Office will be completely eliminated. This should result in a much more timely production of the book.

Data management activities in other areas for the EPESE continue at a very high level. In addition to the semiannual submission of corrected data for the baseline survey, the first and second telephone follow-ups, and end-point data (mortality, hospitalizations, and nursing home stays), we are now collecting data that indicate follow-up status for every year of the study and the occurrence of endpoints. Submissions of data for the first face-to-face follow-up are also underway. Duke will soon submit its first data, preliminary data for the baseline survey.

All tape formats for EPESE have undergone revision this year. All data files now contain the same core information such as age and sex in the beginning of each record. In the files containing questionnaire data, the core section is followed by the common section containing data which all the centers have. Each file ends with a supplement of the remaining data. All data are arranged by subject and the order of the subjects is the same for all files.



A new undertaking--an item file for the EPESE questionnaires--will soon be prepared by this office. This file will be ordered by subject as in the formats and by item within subject categories. This file will also indicate each questionnaire that the item appears in. The item numbers will be the same as those on the formats, thus making it easy to find in the formats. This will be a major activity as thousands of questions are involved.

The programming staff has researched and requested purchase of 18 additional personal computers to make available personal computing power to every EDB staff member. As the machines arrive, Ms. Lafferty will be responsible for installation of the equipment and orienting the staff to its use. In addition two of the new PC's have extra memory and disk storage capacity for more efficient use in graphics and statistical computing. We continue to strive for improved in-house capability in these two areas.

EPESE data analysis has continued in the areas outlined in last year's Sourcebook with some additional new starts. Mr. Foley has been working with data on incidence of nursing home stays, having recently extended the analysis to 3 years of follow-up. This allows for more incident cases in the analysis, providing more statistical power. A manuscript is currently being drafted for submission for publication early in FY 1988. In similar fashion, Dr. Brock, chairman of the EPESE Mortality Endpoint Committee, has been working with EPESE prospective mortality data, also extending the analysis to 3 years of follow-up. Prediction of mortality rates depended on individuals' age, sex, and functional status at baseline for all three centers, but required adjustment of the data for missing physical function items and for the effects of proxy respondents in order to obtain comparable information at all three sites. Having solved those and other methodological problems, the committee is drafting a manuscript for submission in the fall. Two other mortality analyses are underway, one involving the relationship of baseline blood pressure measurements to subsequent mortality, and the other--just beginning--relating smoking and alcohol consumption to subsequent mortality. Initially these analyses will be based on 3 years' mortality follow-up data, although questions persist about potential biases in the exposure data, especially for smoking and alcohol, even with 3 years of follow-up. Drs. Brock, Huntley, and LaCroix are participating in these analyses.

The EPESE Documentation Committee, chaired by Dr. Brock, has continued its work in standardizing documentation for all EPESE data collection, editing, and processing activities. As mentioned above, new formats for data sets have been developed and communicated to the centers through the committee members. The committee has been working with the hospitalization committee in developing useful definitions for hospitalization endpoint analysis. Further, the development of the follow-up status files has continued, as has the integration of activities with the Duke center which will be submitting its baseline survey data soon. As in the past, Ms. Cruz continues her staff liaison activities for the Publications Committee and Mr. Foley continues to serve as a member of the Questionnaire Committee



which recently completed its work in assembling questions for the 1988 in-home interview. Mr. Foley provides consultation on the OMB clearance process on an as-needed basis.

Biometry staff have stepped up activity in the analysis of data from NHEFS with anticipated public release of these data later this year. Mr. Everett presented a paper on the prognostic significance of joint disorders at baseline related to symptomatology at follow-up to the Gerontological Society meeting last November in Chicago. He presented nutrition data on food group intake in the elderly, relating baseline and follow-up interviews to the annual meeting of the Federation of American Societies for Experimental Biology in March, 1987. He made two presentations on arthritis and musculoskeletal data from the NHANES I to the American Rheumatism Association meetings in June, 1987. He presented NHEFS Follow-up data on mortality related to osteoarthritis of the knee in females to the annual meeting of the Society for Epidemiologic Research, also in June, 1987.

In addition to the above analyses, Mr. Everett has participated in the writing of the chapter on arthritis to be included in the NHEFS book entitled, "Health Status and Well-being of the Elderly" to be published later this year. He has completed a draft manuscript on the association of weight and weight history with morbidity and mortality, in collaboration with other EDB staff, NCHS personnel, and NCI researchers. He has participated in the writing of the chapter on nutrition for the NHEFS book (see above), as well as two papers which were spin-offs from that chapter. Finally, he has led the analysis for two papers dealing with methodological issues related to self-reports of body weight in the NHANES. Results on the accuracy of retrospective reporting of body weight will be presented at the upcoming meeting of the American Public Health Association.

Ms. Losonczy has collaborated actively with Dr. White in the preparation of the chapter on cerebrovascular disease for the NHEFS book referred to above. In addition to this chapter, papers on risk factors for stroke and on mortality subsequent to stroke are underway. The statistical analysis involved in these projects required extensive use of not only the questionnaire data, but also data on hospitalizations and mortality in order to accomplish the complicated task of correctly classifying reported cerebrovascular disease into the appropriate categories. In addition to the various analyses related to stroke, Ms. Losonczy has worked with researchers from the University of North Carolina on analysis of dietary patterns and self-perceived health using data from the NHANES and NHEFS.

Mr. Foley has led the analytic effort in the preparation of the NHEFS book chapter on physical functioning and mortality. A statistical model was fitted to data on functional limitations and mortality as multiple responses, with age, sex, race, and presence of self-reported arthritis as explanatory variables. In addition, the analysis was adjusted for the variable length of follow-up which applied to the NHANES respondents, since that variable had a significant effect on both mortality and disability outcomes. A seminar on this topic was presented to analytic staff at NCHS.





The Survey of the Last Days of Life (AG-2-2137) has now been completed, and final data have been received from the contractor, as well as a report describing in full detail the methodology used in the design and conduct of the survey. Biometry Office staff are currently working with the data to verify and edit the questionnaire, pain medications, death certificate, and refusal portions of the data set. Dr. Brock presented preliminary data from the study last November at the conference entitled, "Death on Your Balance Sheet: Costs and Choices in Terminal Care for the Elderly" at the University of Hartford in Connecticut. He will present an overview of the survey and the first final data from the study at the upcoming American Statistical Association meeting. Once the final checking of the data is complete, Dr. Brock, Mr. Foley and Dr. White will be conducting analyses in several content areas including the circumstances surrounding death, transitions between home and various health care settings in the last 3 months of life, decline in physical and cognitive function and presence of symptoms in the last year of life, use of pain medications in the last month of life, and lifetime period prevalence of conditions associated with dying, but not necessarily causing death. In addition, analyses will be conducted on economic variables collected for those decedents who spent time in a hospital or nursing home in the last month of life. These analyses will be led by Dr. Cartwright, in collaboration with Dr. Robert Buchanan, a Robert Wood Johnson Foundation Fellow who is currently at Cornell University.

The National Mortality Followback Survey has continued data collection throughout FY 1987. This survey, supported by an interagency agreement with NCHS (AG-5-0057), is based on a sample of 20,000 death certificates recorded during calendar year 1986 in the NCHS Current Mortality Sample. Mail questionnaires are sent to the next-of-kin of the deceased approximately 5 months after the date of death, with follow-up of nonrespondents by telephone or personal interview. In the first three quarters of data collection a response rate of 89 percent has been achieved. The content of this study is related in some ways to our Survey of the Last Days of Life, particularly in regard to use of nursing homes and cognitive functioning in the last year of life.

The data collection for this study will continue into FY 1988, and it is now estimated that a data tape will be made available to the EDB Program in the fall of 1988. We are now in the process of executing a small add-on to the interagency agreement to provide support for a reinterview of a sample of responses for the purpose of estimating the reliability of the responses received, and to exercise quality control over the field data collection.

Analysis and publication of data on aging have continued in other areas as well as the ones already mentioned. Mr. Foley has collaborated with Dr. Miles of the Epidemiology Office in the preparation of a paper reporting correlates of poor outcomes in cardiopulmonary resuscitation as reported in the NCHS National Hospital Discharge Survey. Dr. Guralnik, Dr. Brock, and Dr. Jacob Brody have collaborated on an article describing demographic characteristics of the U.S. elderly population. Further,



Dr. Brock has collaborated with Dr. Brody and Dr. Williams on an article on trends in the health of the elderly population, published in the 1987 Annual Review of Public Health. Also, Dr. Brock has worked with Drs. Huntley, White and Cartwright on a chapter describing the development of the EDB research program for a book being edited by Dr. George Maddox of Duke University.

Methodologic development continues to be a major concern of the Biometry Office. In FY 1986 we entered into an interagency agreement with NICHD to support a research contract with Research Triangle Institute for development of methods of multiple linear regression analysis appropriate for data derived from complex sample surveys such as the NHANES and the Yale and Duke EPESE surveys. This project has taken the form of improved statistical models for such analyses and applications to relevant data sets along with computer software for implementing the improved procedures. The contractors have completed work on the development of the methods, and we will soon illustrate them with a reanalysis of an NHANES data set relating baseline bone density measures and vitamin D intake to hearing loss in the NHANES respondents.

A project related to the one on regression analysis is the development of improved statistical software for analysis of complex sample survey data. Approval has been obtained for an interagency agreement with NCHS to support a contract for this project. The results of the regression analysis contract will be incorporated into the resulting software package as well as improved methods for conducting epidemiologic analyses on complex survey data in addition to standard NCHS analytical requirements. This package will be extremely useful in allowing more statistically rigorous analysis of data from several sources which involve complex sample surveys.

Another area of interest in methodology is the effect of missing responses in surveys. Last year we reported on the application of statistical models which identify patterns in the missing responses in the Iowa EPESE baseline survey. That work has continued with a Professional Services Contract carried out by Dr. Robert Woolson at the University of Iowa, who compared four methods of estimation for treating incomplete data in the CES-D depression scale as measured in the Iowa EPESE baseline survey. Results illustrate that when pairwise associations between elements in the 11-item scale are of interest, estimation based on developed factor scales performed well as compared to a more complicated estimation scheme based on what is known as the E-M algorithm. Overall, however, the E-M algorithm applied separately to each sex was the preferred method of treating the incomplete data.

A second missing data effect has been seen in the analysis relating EPESE baseline physical functioning measures to subsequent mortality. In Iowa and East Boston, for example, males with missing physical function items had higher mortality rates than those with complete data, whereas for females the opposite was true. This led to the construction of statistical models which corrected for missing data in the scales in order to avoid prediction models with interactions among age, sex, and physical



functioning scores. The missing data effects appear to be strongest in the first years of follow-up, gradually diminishing as more years of follow-up data are obtained.

#### Research Highlights, FY 1987

- Analysis of EPESE mortality data has continued. The ADL, Rosow-Breslau and Nagi physical function scales are all predictive of mortality at 3 years after baseline in each of the first three EPESE locations. In addition, there is a strong differential effect of missing items in all three scales, with individuals showing higher rates of mortality when items are missing than for those whose responses are complete among males. For women the opposite is true, namely, that women with missing scale items have lower 3-year mortality rates than those with complete physical functioning data. The implications of these findings are that subsequent analyses of mortality data should take into account the amount of missing data in the predictor variables.
- EPESE nursing home use data have been extended to 3 years of follow-up. The patterns of use are similar in Iowa and New Haven, but lower rates have been observed in East Boston, possibly because of an active home care program in that community. Mortality rates among nursing home users appear to be higher than the rates for each community as a whole--an expected result.
- Analysis of a disability index used in the NHEFS shows higher rates of disability and mortality for those individuals with higher index scores. Other factors influencing these outcomes include age, race, sex, and reported presence of arthritis at baseline.
- Analysis of NHEFS data has shown an influence of baseline reports of knee pain and radiographic abnormalities on subsequent symptomatology, disability, and mortality as measured at follow-up.
- Preliminary results are now available from the Survey of the Last Days of Life. Among lifetime period prevalence rates in the sample of decedents were 6 percent with a report of blindness, 8 percent with deafness and slightly more than 8 percent with a reported physician diagnosis of Alzheimer disease or other types of dementia. Other findings showed that more than half the deaths took place at a hospital, approximately one-fifth at home, and the remainder at other residential settings such as nursing home or hospice. More than half the decedents were reported to have died in their sleep and more than 90 percent saw various members of their families in the last 3 days of life. More than half the decedents were reported to have been in good or excellent health one year before death, a figure that declined to one-fourth the month before death and one-eighth the day before death occurred.
- Results of a methodologic study of nonresponse in the Iowa EPESE baseline survey showed patterns in the types of nonresponse which



indicate that the data are not missing at random, that in fact, responses are affected by the respondent's age, sex, marital status, and in some instances, whether they had experienced certain medical conditions, such as heart disease or hypertension. The implications of these results are that caution must be exercised in the treatment of missing data for the analysis of the EPESE baseline survey and in the use of baseline measures as possible predictors of subsequent outcomes.





## CONTRACT

Name and Number: DMH ASSOCIATES, INC. (NO1-AG-2-2137)

Title: Survey of the Last Days of Life

Date Contract Initiated: September 30, 1982

Total Cost of Contract: \$443,576

**Objectives:** The purpose of this project is to collect descriptive data on the last days of life for a community sample of persons age 65 and older whose deaths occurred in a one-year period. In addition to providing specific data on basic events and circumstances surrounding death, the study provides lifetime prevalence data for a set of conditions related to, but not necessarily causing death.

**Methods Employed:** A sample of death certificates will be selected over a period of one year in Fairfield County, Connecticut. Retrospective information concerning the decedent's last days of life will be obtained in a face-to-face interview with an informant identified from the information contained on the death certificate. Follow-up information will be obtained from medical sources identified by the informant for those cases in which it is appropriate.

**Major Findings:** Among lifetime period prevalence rates in the sample of decedents were 6 percent with a report of blindness, 8 percent with deafness and slightly more than 8 percent with a reported physician diagnosis of Alzheimer disease or other types of dementia. Other findings showed that more than half the deaths took place at a hospital, approximately one-fifth at home, and the remainder at other residential settings such as nursing home or hospice. More than half the decedents were reported to have died in their sleep and more than 90 percent saw various members of their families in the last three days of life. More than half of the decedents were reported to have been in good or excellent health one year before death, a figure that declined to one-fourth the month before death and one-eighth the day before death occurred.

**Significance to Biomedical Research:** A considerable body of literature exists in the geriatric and psychological fields as well as in the lay press about dying. Yet specific data about basic events associated with dying are lacking--such as who dies peacefully in his/her sleep, who dies in great pain, what persons are present at the time of death, who dies after a long illness with full awareness of his impending demise, and who dies suddenly with no warning. Further, the proportion of the dying who need and actually receive pain medication is unknown. The study provides an opportunity to obtain epidemiological data on the numbers of persons affected by the major health conditions that confront the dying elderly as well as the lifetime likelihood of certain events and conditions such as blindness, deafness, dementia, hip fracture, and others.

**Proposed Course:** Preliminary data was presented at a conference entitled, "Death on Your Balance Sheet: Costs and Choices in Terminal Care for the Elderly" at the University of Hartford in Connecticut. An overview of the



survey and the first final data from the study was presented at the American Statistical Association meeting. Once the final checking of the data is complete, analyses will be conducted in several content areas including the circumstances surrounding death, transitions between home and various health care settings in the last 3 months of life, decline in physical and cognitive function and presence of symptoms in the last year of life, use of pain medications in the last month of life, and lifetime period prevalence of conditions associated with dying, but not necessarily causing death. In addition, analyses will be conducted on economic variables collected for those decedents who spent time in a hospital or nursing home in the last month of life.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 06060 03 EDBP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

National Mortality Followback Survey

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D.,  
Chief, Biometry Office, EDBP, NIA

## COOPERATING UNITS (if any)

National Center for Health Statistics

## LAB/BRANCH

Biometry Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This survey is based on a sample of 20,000 death certificates recorded during calendar year 1986 in the NCHS Current Mortality Sample. Mail questionnaires are sent to the next-of-kin of the deceased approximately five months after the date of death, with follow-up of nonrespondents by telephone or personal interview. In the first three quarters of data collection a response rate of 89 percent has been achieved. The data collection for this study will continue into FY 1988, and it is now estimated that a data tape will be made available to the EDB Program in the fall of 1988. We are now in the process of executing a small add-on to the interagency agreement to provide support for a reinterview of a sample of responses for the purpose of estimating the reliability of the responses received, and to exercise quality control over the field data collection.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 06070 02 EDBP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Multiple Linear Regression Analysis

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dwight B. Brock, Ph.D., Chief, Biometry Office, EDBP, NIA

Barry I. Graubard, M.S., Mathematical Statistician, EBRP, NICHD

## COOPERATING UNITS (if any)

National Institute of Child Health and Human Development

## LAB/BRANCH

Biometry Office

## SECTION

Epidemiology, Demography, and Biometry Program

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The National Health and Nutrition Examination Survey (NHANES) I and its Follow-up form an integral part of the NIA EDB scientific data base. More than 100 different analyses are planned by EDB and its collaborators. To make appropriate use of these data in regression analyses, adjustments must be made in usual regression techniques because the data from these complex samples do not meet the assumptions required by ordinary regression analysis.

The purpose of the project is to study and develop statistical methodology for multiple linear regression models that can be appropriately applied to the NHANES. The NIA entered into an agreement with NICHD for the purpose of expanding the scope of the contract with the Research Triangle Institute to develop statistical methodology for multiple linear regression models that can be appropriately applied to data from the NHANES and its Follow-up Survey.

The contractors have completed work on the development of the methods, and we will soon illustrate them with a reanalysis of an NHANES data set relating baseline bone density measures and vitamin D intake to hearing loss in the NHANES respondents.

EDBP-36



## ANNUAL REPORT OF THE OFFICE OF THE SCIENTIFIC DIRECTOR

### NATIONAL INSTITUTE ON AGING

The Intramural Research Program has made considerable gains during the past year in its effort to remain in the forefront of gerontological research. A number of our staff have received honors or special recognition for their contributions as professionals and as scientists.

Leading the parade of honorees, Dr. Reubin Andres received both the Allied-Signal Achievement in Aging Award last December and the Enrico Greppi Prize of the Italian Society of Gerontology and Geriatrics this September. In the Laboratory of Behavioral Sciences, Dr. Bernard T. Engel was an invited speaker before the Second World Congress of Neurosciences in Budapest, Hungary, as was Dr. Robert Friedland of the Laboratory of Neurosciences. LBS' Dr. Kathleen McCormick was honored by the American Lung Association of Maryland as its volunteer of the year and also received an award from the Association of Military Surgeons of the United States.

Dr. Richard G. Cutler of the Laboratory of Cellular and Molecular Biology was elected the 1988 chair of the Biological Sciences Section of the Gerontological Society of America. Dr. James L. Fozard, Associate Scientific Director for the BLSA, received a Certificate of Appreciation and Recognition from the AMA Task Group on Dementia. Staff of the Laboratory of Personality and Cognition, in addition to being named fellows in several organizations, also have distinguished themselves serving as editors or consulting editors on no less than five important psychological journals.

Scientific achievements this year have been many as shown in the total annual report document. However, a few of the many noteworthy accomplishments should be highlighted here.

- o For a number of years, the Laboratory of Behavioral Sciences has conducted an outpatient continence treatment program. This program has proven an outstanding success scientifically and therapeutically. There has been a proliferation of continence treatment clinics patterned after the NIA model developed here in Baltimore, both in this country and abroad. These clinics' staff received training and advice directly from staff of LBS investigators. The research goals of this study have been accomplished, its practicality proven, and on this high note, the outpatient program will now end.
- o Investigators in the Immunology Section of the Laboratory of Clinical Physiology have noted a marked decline in the number of lymphocytes, beginning three years prior to death in a 16 year longitudinal study of 105 elderly men who are participants in the Baltimore Longitudinal Study of Aging (BLSA). All the men were considered healthy at the initiation of the study. The IRP scientists sought to assess the relationship between declining immunity and mortality. In analyzing records of the 105 men following their deaths, the investigators found that beginning three years before death, lymphocytes began declining progressively in the subjects. Interestingly, the decline noted was not associated with either age at time of death or with the cause of death.



- o BLSA analysis of vision and hearing declines over time have demonstrated gradual declines longitudinally in visual acuity. Over a 14-year testing phase, males from their twenties into their eighties were examined for near and far visual acuity. The findings suggest that modest declines in visual acuity occur across the entire age spectrum in subjects with both corrected and uncorrected vision. Most major changes, however, were seen in males in their sixties or seventies when first tested. Greater losses in visual keenness occurred in subjects who initially had the best acuity. A 10-year assessment of hearing thresholds in hundreds of BLSA subjects showed that age changes in hearing occur in all aged groups (20-80s). These findings show that "normal" hearing loss occurs over the entire hearing frequency spectrum, although this type of hearing deficit may not become self-apparent until mid or later life.
- o A long time administrative goal of the Baltimore Longitudinal Study of Aging (BLSA), has been to have the female cohort equal in number the size of the male sample. This should be achieved early in the new fiscal year when the number of women is expected to reach 550, approximately the same size as the active male population. This equality of numbers should make possible more accurate measurement of age changes and/or differences between males and females in the Study.
- o Researchers in the Laboratory of Cardiovascular Science have noted that maximum oxygen consumption at exhaustion during bicycle exercise in male senior athletes greatly exceeds that of sedentary age matched men (ages 60-75 years). However, cardiac output, measured via gated blood pool scans, did not vary substantially between the two groups. Thus, the enhanced  $\dot{V}O_{2\max}$  due to physical conditioning is attributed to a greater peripheral tissue  $O_2$  extraction. Conversely, diminished  $\dot{V}O_2$  during aerobic exercise in elderly sedentary men is, to a substantial extent, peripheral rather than cardiac in nature.
- o Research in the Laboratory of Cellular and Molecular Biology on the age-related metal increase of zinc in aging human diploid fibroblasts indicates that in vitro aging leads to a much higher accumulation of zinc in the cell nucleus than in the cytoplasm. When cells are challenged with toxic zinc levels, most of this metal penetrates the nucleus. The greater effect on the nucleus probably is due to a higher permeability of the nucleus with cellular aging.
- o A clinical study by endocrinologists in the Laboratory of Clinical Physiology has demonstrated that prevailing plasma levels of estradiol and testosterone (sex steroids) do not predict development of coronary artery disease in men, nor do sex hormone levels correlate with known risk factors for heart disease. This apparently debunks a widely held notion that, in men, there is a positive association between endogenous estradiol levels and premature development of coronary heart disease.
- o Longitudinal studies of patients with dementia of the Alzheimer type (DAT) confirmed cross-sectional findings by Laboratory of Neurosciences' researchers showing that neocortical metabolic changes precede neurocortically-mediated neuropsychological impairments in early DAT. The brain is capable of compensating for these early physiological changes in DAT to maintain premorbid neuropsychological functions.





## ADMINISTRATIVE SERVICES

Administrative services comprise two distinct units which provide a wide range of support services essential to the effective operation of the Intramural Research Program. These are the Administrative Office and the Procurement/Receiving Unit.

The Administrative Office in Baltimore functions in a very different manner than that of other institutes due to the distance from the NIH complex and the need to operate and maintain a separate facility. In FY 1987, as in past years, this office was responsible for budget management, station support, contract monitoring and administration, building operations, travel review and authorization, property accountability, administrative reporting, personnel ceilings, time-keeping and payroll activities, imprest fund disbursements and recordkeeping, space management, telephone service, training, and safety. Staff also participated in various intramural committees important for the internal governance of the IRP.

The Procurement/Receiving Unit reports directly to the Administrative Officer and bears responsibility for the direct purchase and receipt of all procurement actions within the delegated authority of \$5,000, and the monitoring of all requisitions sent to NIH Central Procurement for the IRP Gerontology Research Center (GRC). Materials received must be checked against ordering information and then distributed to appropriate areas.

This office also is responsible for twice weekly trips to the NIH for pickup and delivery of supplies and materials as well as trips in the local area to procure over-the-counter emergency supplies. In addition, the unit picks up incoming mail from the Francis Scott Key Medical Center mail room and must distribute this mail twice daily.

Highlight activities of these two administrative service components follow.

### Administrative Office

- o A total of approximately 26,000 budget line items were logged into the records system this year as part of IRP budget management. Spending levels were reviewed to make sure research areas kept within allocated budget funds.
- o Weekly and monthly NIH accounting reports were verified against in-house records to provide IRP chiefs with information to help plan program expenditures.
- o Administered a number of contracts providing building services such as housekeeping, security, building maintenance (heating/air conditioning/ventilation), utilities, waste disposal--general and radioactive, and radiation control.
- o The GRC property representative conducted the annual inventory of 3,461 property items. Documentation was prepared and processed for surplus of 211 items of property, receipt and decal of 482 items, and transfers between IRP custodial codes of 686 equipment items.





- o Monitored FTE usage and prepared reports for the Scientific Director's use and the NIA Budget Office to comply with personnel ceiling.
- o Reviewed personnel action requests before submission to the Scientific Director and after approval initiated 457 Requests for Personnel Action and processed same between August 1986 and July 1987.
- o Reviewed, approved and processed some 925 travel orders, vouchers, or 348's during the year.
- o Prepared, processed and got approvals for 115 training documents and helped organize several in-house training courses for the IRP staff.
- o Managed and maintained a \$3,000 imprest petty cash fund used for emergency supplies and materials, payment of seminar speakers, research participant payments, and emergency travel advances. Over the year, 536 petty cash transactions were handled.
- o Aided and provided support for other activities including space renovation, work on completion of the body density laboratory, and preparation and entry of 500 ID key cards for the new security system.

#### Procurement/Receiving Unit

- o Processed 1,188 purchase orders and 25 telephone charge orders.
- o Handled 2,628 blanket purchase order record of calls and 70 reprint orders.
- o The Unit handled all phases of 61 repair orders and issued 480 petty cash vouchers.
- o A total of 891 stock requisitions were made.
- o GRC/IRP delegated procurement authority was increased from \$2,500 to \$5,000 this fiscal year.



NATIONAL INSTITUTE ON AGING  
Intramural Research Program

Information Services

The Intramural Information Office activities during fiscal year 1987 encompassed a wide variety of activities from preparing articles for the NIH Centennial and JAMA, to editing a history of the International Association of Gerontology, to coordinating the annual report, the annual Combined Federal Campaign, employee recognition programs, and handling numerous contacts with the media and public sector.

The Information Office undertook a number of writing and editorial assignments during the year. An article on declining peripheral lymphocytes with aging was prepared for the "From the NIH" column of JAMA; another on age-related sensory changes was published in the widely circulated NEWS AND FEATURES FROM NIH. Under an informal agreement, three articles on activities of the Baltimore Longitudinal Study of Aging (BLSA) were written for the Human Factors Society newsletter. Two issues of an information letter to BLSA participants were sent out during the year, with a third currently in preparation. Several items on intramural research were also written for various NIH Centennial publications or information kits.

In addition, the office prepared and distributed 12 issues of the internal newsletter GERON-NEWS, summarized the voluminous intramural annual report for distribution to the National Advisory Council on Aging, handled revisions of the Medical Staff Fellow Program and Summer Research Fellow catalogs, and prepared a fact sheet for visitors to the intramural research center in Baltimore.

In the area of outreach education, the Information Office staff directly addressed nearly 760 individuals by means of outside speaking engagements, college lectures, briefings and tours at the Gerontology Research Center, or via programs arranged for specific groups. The audiences for these programs included professional service providers, university faculty and staff, high school biology teachers, both undergraduate and graduate nursing students, volunteer groups, aging research foundations, and foreign visitors from countries including China, France, Israel, and Japan. Special laboratory demonstrations and tours were also arranged for attendees at the NIA Summer Institute on Aging and for top high school science students attending the annual Maryland Junior Science and Humanities Symposium.

Major media efforts during the year included setting up two days of filming at the Gerontology Research Center for WRC-TV Channel 4 (Washington); helping with a story on the BLSA for WJZ-TV Channel 13 (Baltimore); arranging for filming and interviews for "Aging 2000," an Australian TV production scheduled to be imported to the United States in the near future; and, working with Peter Hackes for a "Modern Maturity" segment aired over a number of PBS-TV stations nationwide.



Other media assistance during fiscal year 1987 included that given to THE SACRAMENTO BEE (Reagan's health and age); RUNNER'S WORLD (bone research); British radio's "Help for the Aged" show; UPI (article on hyperthermia); OMNI (BLSA); USA TODAY (exercise); and, WASHINGTON POST (human aging). Contacts also made by and with NEWSWEEK, READER'S DIGEST, GENTLEMAN'S QUARTERLY, WOMEN'S DAY, LOS ANGELES TIMES, VOGUE, CINCINNATI ENQUIRER, and GOOD HEALTH MAGAZINE. Specialty aging or health contacts were made with MATURITY NEWS SERVICE, TODAY'S NURSING HOME, GRANDPARENTS, 50 PLUS, MEDICAL WORLD NEWS, HEALTHSCENE, HIPPOCRATES, AND BIOSCIENCE.

Some of the special activities engaged in by the Information Office this year included co-sponsoring, with the Francis Scott Key Medical Center Volunteer Department, a workshop for the community entitled "Survival After Sixty." This office prepared the program, helped with publicity, supplied meeting rooms, and gave tours to attendees.

Also, the Communications Officer worked closely with the editor of EXPERIMENTAL GERONTOLOGY on the special two-volume issue of the journal honoring NIH Scientist Emeritus, Dr. Nathan W. Shock. Suggestions were made for authors, names provided for invitations for a ceremony to present the issue to Dr. Shock, and all arrangements for the event were made by this office.

In addition to the above, the Information Office set up an orientation program for new employees of NIA and the IRP; did publicity, reports and served as overall coordinator for the 1986 Combined Federal Campaign; and ran two Red Cross Blood Drives during the year.

The Communications Officer also prepared flyers, a program, and designed a poster for the Federal Executive Board's fall 1986 Employ the Handicapped Conference, and designed and printed the program for the Baltimore Federal Executive Board's first Barrier Awareness Day, serving as master of ceremonies for the event.

IO staff also were involved actively in several organizations this year. The Communications Officer was elected to the Maryland Gerontological Association's Board of Directors, as PHS Handicapped Employees Advisory Committee Secretary, and was appointed editor of the MGA's newsletter. His activity with handicapped activities earned him a certificate of appreciation from the Baltimore Federal Executive Board. Staff also served as recording secretary for the IRP ad hoc committee for working relations and for the monthly Branch/Laboratory/Section Chiefs' meetings.

IRP Information activities for FY 1987 are highlighted below.

#### Articles/Publications/Editorial

- o Researched and wrote article on declining peripheral lymphocytes with age for JAMA's "From the NIH" column.
- o Engaged in lengthy concept clearance effort with DHHS for revision of Research Training Opportunities at the NIA, now in draft stage.





- o Wrote article on age-related sensory changes which was published in NEWS AND FEATURES FROM NIH as part of a special aging issue for the NIH Centennial.
- o Prepared piece on the BLSA and normal human aging for the NIH Centennial research accomplishments packet.
- o Article on Dr. Andres' Allied-Signal award prepared for NIH RECORD.
- o Researched and prepared IRP Annual Report Summary for NACA presentation.
- o Research highlight articles on the BLSA were prepared for three issues of the Human Factors Society newsletter.
- o Prepared short fact sheet on IRP for visitors to the Baltimore Center.
- o Coordinated and prepared annual revision of Medical Staff Fellow and Summer Research Fellow catalogs published by NIH.
- o Wrote draft of letter to NEWSWEEK correcting errors and omission of NIA activities in summer 1986 article on aging.
- o Publicized NIA and its IRP activities in the Maryland Gerontological Association Newsletter, including coverage of the NIA Centenarians Day program (July 1987).
- o Helped arrange interviews and edited special articles being prepared for Francis Scott Key Medical Center's magazine, KEYNOTES.
- o Editorial Assistant did extensive work on Scientist Emeritus book detailing history of the International Association of Gerontology to be published by Springer. Communications Officer spent considerable time proofing and editing the manuscript.
- o Staff provided extensive editorial assistance to the Laboratories of Behavioral Sciences, Cardiovascular Science, and Clinical Physiology.
- o Staff wrote, edited and distributed 12 issues of GERON NEWS.
- o Jan Ehrman gathered information and wrote two issues of newsletter for BLSA participants, PAGES OF THE AGES, and has started on a fall issue.
- o The Communications Officer wrote and edited two issues of the MGA newsletter and four issues of the Maryland Hospital Public Relations Society letter, GALLIMAUFREY.

### Special Projects

- o Communications Officer chaired IRP Combined Federal Campaign drive, including publicity, reports, etc. Achieved 118% of dollar goal.
- o Publicized, organized, ran two Red Cross Blood Drives (116 units).



- o Co-chaired publicity and served as photographer for Baltimore Federal Executive Board Employ the Handicapped Conference (October 1986).
- o Arranged for awards, folders, publicity for IRP Awards Ceremony.
- o Provided internal and external publicity help for NIH Handicapped Employees Committee 1986 NIH celebration of Employ the Handicapped program.
- o Worked closely with Leonard Hayflick, editor of EXPERIMENTAL GERONTOLOGY on logistics, invitations, operation of special program honoring Dr. Nathan W. Shock with two-volume set of Experimental Gerontology.
- o Served as photographer for celebration of first anniversary of the joint NIA/FSKMC Senior Athlete's Study. Story and pix for GERON NEWS.
- o Arranged laboratory demonstrations and provided information kits for annual Maryland Junior Science Symposium.
- o Set up laboratory demonstrations/tours and provided guides for NIA Summer Institute on Aging participants.
- o Served as FY 1987 Annual Report coordinators, providing secretarial training session, as well as normal logistics support.
- o Carried out publicity, designed and printed program and served as Master of Ceremonies for first Baltimore celebration of Barrier Awareness Day held by Baltimore Federal Executive Board (May 1987).
- o Assisted NIA PIO with slides/interviews in connection with July 1987 NIH Centennial aging symposium sponsored by NIA. Also provided transportation from Baltimore to Bethesda for principle speaker.
- o Helped co-sponsor Francis Scott Key volunteer workshop for community, "Survival After 60," preparing program, publicity, and providing tours.
- o Jan Ehrman helped set up an IRP orientation program for 35 Summer Aids, and other new GRC or NIA employees (August 1987).
- o Information Office prepared an extensive list of potential invitees for NIA Assistant Director for Special Programs in connection with the NIA. Florence Mohoney lecture (Fall 1987)
- o IO served as coordinator for preparation of NIH annual directory and bibliography (December 1986).

#### Outreach Education

- o CO was the luncheon speaker for meeting of Wheaton chapter of NARFE held in Rockville, Maryland.



- o Jan Ehrman spoke on aging research for "Family Night" at the Randolph Hills Nursing Home in Wheaton, Maryland.
- o Dan Rogers was the evening's speaker for a dinner honoring volunteers of the Manor Care Nursing Home, Rossville Boulevard, Baltimore.
- o Another lecture on aging was given by the CO at Goucher College evening school.
- o Two evening talks on aging research were given (one Fall 1986 and one Spring 1987) to sociology/psychology students of Dundalk Community College.
- o Jan Ehrman spoke on the topic, "Aging is not a Disease," at the Jewish Community Center, Rockville, Maryland, (September 1987).
- o The Communications Officer supplied handouts and helped staff exhibit for Francis Scott Key Health Fair held at Southeastern Elementary School.
- o Briefed 13 social workers from the Arlington (VA) Bureau of Services to the Elderly and Handicapped.
- o Arranged special program, briefing, tour for 29 church volunteers from Syracuse, New York, at request of Hopkins' Dr. Matthew Tayback.
- o Briefed several visitors from Florida Federation of Aging Research, Alliance for Aging Research, and the Dome Corporation.
- o Hosted several groups of foreign visitors from Japan, China, France, and Israel.
- o Held number of programs at the GRC for nurses from Georgetown University, St. Joseph's Hospital, University of Maryland, University of Virginia, and staff from several VA centers.
- o Arranged briefing and tour for attendees at the National Association of Biology Teachers meeting being held in Baltimore.

#### Media Interaction

- o Discussed aging generally with SACRAMENTO BEE for article on President Reagan.
- o Arranged for two-day filming of BLSA and GRC programs for WRC-TV.
- o Coordinated filming in Molecular Physiology Section for Toronto TV.
- o Cooperated with RUNNER'S WORLD supplying photographic material for story on bones/osteoporosis research.
- o Provided material to new women's health newsletter, BODY KNOWLEDGE.



- o Arranged for interviews, BLSA subject, and filming of BLSA for "Senior Report," aired weekly by WJZ-TV Channel 13 in Baltimore.
- o Helped arrange interviews and set up filming by CNN News for incontinence study.
- o Made arrangement for interviews and set up filming for new Australian TV program, "Aging 2000."
- o Provided background and arranged interviews for British radio.
- o Worked with USA TODAY providing information for article on exercise.
- o Provided logistics support and guidance for PBS "Modern Maturity" segment on the BLSA with Peter Hackes.
- o Material on hyperthermia was provided for a UPI article on the subject.
- o Made plans to help WQED-TV, Los Angeles film GRC laboratories (Fall 1987).
- o Made contacts throughout the year with NEWSWEEK, BALTIMORE SUN, GOOD HEALTH MAGAZINE (NYT), READER'S DIGEST, INSIGHT, THE WASHINGTON TIMES, WASHINGTON POST, GENTLEMAN'S QUARTERLY, WOMEN'S DAY, VOGUE, CINCINNATI ENQUIRER, LOS ANGELES TIMES, and others.
- o Health or aging field contacts were made with BIOSCIENCE, GRANDPARENTS, MATURITY NEWS SERVICE (NYT Syndicated), HEALTHSCENE, HIPPOCRATES, MEDICAL WORLD NEWS, and TODAY'S NURSING HOME.
- o Supplied extensive background to Dallas physician for TV appearance dealing with aging.

### Training

- o Daniel Rogers took part in Chesapeake Public Relations Workshop (October 1986).
- o Mr. Rogers participated in National Association of Government Communicators Annual Conference (November 1986).
- o Communications Officer attended annual Maryland Governors Committee on Employment of the Handicapped Annual Conference (Spring 1987).
- o Jan Ehrman took part in the program, "Geriatric Drug Update."
- o Mr. Rogers attended seminar, "Recognition, Acceptance and Implementation of Safety Responsibilities in Biomedical Research." (June 1987).





#### Other Activities/Honors

- o Communications Officer received Certificate of Appreciation from Baltimore Federal Executive Board for publicity efforts for the FEB Employ the Handicapped Week program in Annapolis, Maryland.
- o CO elected to Maryland Gerontological Association Board of Directors.
- o Mr. Rogers elected secretary for PHS Handicapped Employees Advisory Committee.
- o As Third Vice President and member of the Board of Directors, CO received R and W President's Award for Service (June 1987).
- o Daniel Rogers was appointed Editor of the Maryland Gerontological Association Newsletter and continued to serve as Editor of the Maryland Hospital Public Relations Society Newsletter.
- o Information Office helped set up several employee education programs, including a joint effort with personnel for a workshop on the new W-4 forms; several video showings of aging programs.
- o Staff publicized and assisted with picnics and other activities for FSKMC Mason F. Lord chronic care patients.
- o Mr. Jan Ehrman served on the ad hoc committee for working relations and also as its recording secretary.
- o Operation of R and W photo service provided funds used by the IO to help support the GRC holiday party as well as International Asian Day in Baltimore, and other activities.



NATIONAL INSTITUTE ON AGING  
Intramural Research Program

Information Activities Summary  
October 1, 1986 - September 30, 1986

* SPECIAL PROJECTS .....	19
** ARTICLES/PAPERS/FACT SHEETS .....	14
SPEAKING ENGAGEMENTS/BRIEFINGS/TOURS .....	42
PEOPLE ADDRESSED .....	758
MEDIA INQUIRIES .....	156
MEDIA (INTERNATIONAL) .....	9
REPORTS .....	4
*** NEWSLETTERS .....	20
PUBLIC INQUIRIES (MAIL AND PHONE).....	510
PUBLICATIONS/ARTICLES/REPRINTS DISTRIBUTED .....	6002
* Includes CFC Campaign, 2 Blood Drives, Awards Program, EXPERIMENTAL GERONTOLOGY issue honoring Dr. Shock, special programs arranged for Summer Institute on Aging, and coordination of Annual Report and Annual Bibliography, etc.	
** This covers material prepared for NIH Centennial publications, articles for JAMA, NEWS AND FEATURES FROM NIH, NIH RECORD, Human Factors Society Newsletter, fact sheets, revisions of Medical Staff Fellow Catalog, etc.	
*** Twelve issues of GERON NEWS, two issues of letter to BLSA participants; two issues of MGA NEWS, and four issues of MHPRS newsletter.	



ANNUAL REPORT OF THE RESEARCH RESOURCES BRANCH  
NATIONAL INSTITUTE ON AGING

Technical Development Section

Two disk drives and additional memory, purchased this year for installation next fall, will offset to a minor extent the ever-increasing demands placed upon the central computer system. In addition, the purchase of terminal-servers for a few selected areas provided another step toward our goal of a totally clustered configuration. This arrangement will allow the dynamic balancing of loads on the CPU's, and for much more efficient future expansion.

The major development effort to integrate the various existing graphics software packages and the many different types of graphics devices into a "any-package-talks-to-any-device" environment is complete. As new and different graphic devices arrive at the Center, they are quickly supported. Documentation for elements of this software has been written and made available to the users. The latest arrival is laser printers that support the Postscript language. This language, which appears poised to become an industry standard, allows typeset-quality printing, graphic figures, and pictorial images to be combined onto one page. With the printer's internal character fonts and our software package, users will easily and independently create manuscript-quality figures. Manuscripts and posters with embedded drawings are well within the realm of possibility in the near future. Many graphing programs, available for IBM and Apple Macintosh's, support the Postscript language and will be able to use this type of printer. Any future procurements of high-quality graphics devices, such as film recorders (color slide markers) and color printers, will support these users.

Our efforts to familiarize ourselves with the IBM PC, in order to provide the staff with consultation and interfacing services, continue. To date, we've accomplished the following:

- ° Developed our own laboratory interface using microprocessoe hardware, and techniques that we've developed over the past ten years. The only modification to the PC is the addition of an extremely simple parallel communication card.
- ° Selected Microsoft's Quick Basic as our primary development language.
- ° We have nearly completed our first major job - a PC based system that monitors  $O_2$  consumption,  $CO_2$  production and other measures during treadmill exercise testing. In addition, it supports cardiac output measurements using the accetylene rebreathing method.
- ° Configured a laboratory-based PC as an Ethernet node of the central VAX computer system; allowing extremely fast data transfer.

Photography and Arts Unit

In addition to the normal production of negatives, slides, prints, and poster materials, the computer graphics system was expanded to include the development of new software for use in the unit. This new software enables the unit to produce graphs which closely match almost any type of variation presented





to the unit. Plans are being made to make this software available to any VAX user with the proper hardware. In addition, new hardware has been ordered for the VAX machine room, for use by anyone in the building.

An increased demand for service this past year was matched by an increased capacity from the computer graphics system. A considerable amount of time was saved, not only because some of the work was done by others outside the unit, but also because the time expended on the computer is far less than the time needed for conventional processes.

A MacIntosh system was added to the unit this year. This system will help the unit continue to add to computer graphic's capability.

#### Library Unit

The following achievements were successfully accomplished in FY '87:

- The Librarian performed more than 220 computerized bibliographic searches in 1987. Scientists of two laboratories are already performing their own end-user searches; the statistics actually show an increased demand by the GRC research community. MEDLINE remains the primary data base of information retrieval, and there was a number of searches performed on Chemical Abstract data bases.
- The Center purchased 562 new books in FY '87. Out of these, the Library bought 270 books (totaling \$13,500.00), and other laboratories bought 292 volumes (totaling \$12,000.00).
- 891 inter-library loan requests were made to serve the information needs of intramural scientists. About 90% of the 803 article requests and one quarter of the 88 book loans were provided by the NIH Library. We filled 174 reprint requests for other libraries.
- More than 800 volumes of journals were bound this past year.
- On the current journal shelves, a new arrangement was made, and "aging" related journals are separated from other regular journals.
- On a twice-a-day service schedule provided by the Library staff, a total of 881 volumes of journals were retrieved from the basement storage area, for the usage of library users.

#### Animal Resources Section

The following achievements were successfully accomplished in FY '87:

- Maintained accreditation with the American Association for Accreditation of Laboratory Animal Care (AAALAC) for the 10th consecutive year.
- Maintained institutional membership with the American Association of Laboratory Animal Science (AALAS), as well as with its local National Capital Area Branch (NCAB).
- A total of 5,843 mice and rats, of varying ages, were issued from the aging colonies.



- ° 240 hours were used to support 72 aseptic surgical procedures.
- ° In addition to our stock animals, approximately 5,073 mice, 2,942 rats, 2,500 chicks, 235 rabbits, and 20 primates were received and housed by the ARS.
- ° The ARS was able to supply approximately 165 mice and 60 rats to other institutions throughout the country, for use in research efforts.
- ° A hyperchlorination unit has been added to our existing automatic watering system, to enhance water quality.
- ° 12 aging Beagles have been placed in an exercise program to study the effects of osteoporesis.

#### Instrument, Design, and Fabrication Section

In the past year, along with the many 30 minute to 2 hour construction and repair jobs, the section designed, fabricated, and installed equipment such as a MRI bird cage probe, probes used in exercise physiological studies, dynamometers to interface with PC's, heliarc welding of chairs and ladders for the body density lab, stainless steel laminar flow counter-current barrier well, inclined mouse holder for an automated monitoring device, a beam-splitter and other longer term projects.



## ANNUAL REPORT OF THE LONGITUDINAL STUDIES BRANCH

### NATIONAL INSTITUTE ON AGING

The scientific function of the Longitudinal Studies Branch (LSB), created in FY 1986, is to promote and conduct multidisciplinary, longitudinal studies of physiological and behavioral changes with aging. Its administrative responsibility is for the management of the Baltimore Longitudinal Study of Aging (BLSA), a longstanding research program of the Gerontology Research Center. The administrative and scientific roles of LSB staff are: (a) recruitment and maintenance of the research participants in the BLSA; (b) entering, storing and retrieving BLSA data in computer based data banks; (c) improvement of quality control procedures for BLSA data; (d) conducting research with the BLSA data; and (e) and developing statistical methodologies appropriate to longitudinal studies. The BLSA is utilized by scientists in eleven different sections of eight laboratories. To facilitate coordination of the diverse activities across the numerous organizations, the LSB Chief also holds the title, Associate Scientific Director for the Baltimore Longitudinal Study of Aging, and in that capacity is assigned to the Office of the Scientific Director, NIA. The Associate Scientific Director, in concert with an internally comprised Steering Committee, is responsible for setting long term scientific goals for the BLSA as well as promoting and facilitating the use of the BLSA by scientists within and outside of the Gerontology Research Center.

The research objectives of the LSB relative to the BLSA are:

1. To perform studies of age-related changes in physiological and behavioral functions utilizing both existing information collected on BLSA participants over the life of the Study, and newly started research. In FY 1987 research with existing data was completed in vision, hearing, pulmonary function and reaction time.
2. To perform correlational and retrospective studies that relate BLSA data from various disciplines to one another and to various participant endpoints, e.g., disease, death, and functional disabilities. In FY 1987 research was completed relating death to risk factors for disease.
3. To apply and develop new statistical methodology and theory appropriate to longitudinal studies. In FY 1987 research was completed in the areas of multiple comparisons, time dependent covariates, and regression analysis.
4. To promote and facilitate the use of the unique BLSA research resource by scientists both within the Gerontology Research Center and outside the Institute using either new information or existing data. In FY 1987 eleven new projects were approved and initiated. Forty-six scientific studies are currently being carried out in the BLSA.
5. To develop long range scientific plans which will enhance the value of existing information and provide a scientifically sound basis for eliminating, adding or maintaining current test procedures. In FY 1987 efforts focused on improving information on causes of death of participants and functional disabilities.



6. To provide a stimulating and challenging environment for the research training of scientists of any level whose educational needs can be met by the unique environment offered by a large scale multidisciplinary research endeavor. Two students in statistics research training received several months of training and a psychology graduate student initiated a year long research training program.

The support of the six research objectives stated above requires a relatively complex administrative and management activity. The complexity alluded to results from the facts that: there are several hundred men and women scheduled for dozens of procedures on a recurring two year cycle of testing; there are dozens of investigators, some new and others more senior, whose activities are supported from time of research planning through data collection, storage, and utilization; and there is a very large data bank representing thousands of variables and spanning over a quarter century of data collection efforts.

The five administrative and management objectives for the LSB that support the six research objectives relative to the BLSA are:

1. To improve retention of current research participants in the BLSA through better feedback of information about themselves and the Study, better utilization of time and reduction of required paper work relative to forms and procedures, and improvements in the social and physical environment of the research setting;
2. To maintain the current number of under-75 male participants and to increase the number of female and over-75 male participants in the BLSA;
3. To improve the utilization of participant time in order to increase the opportunities for research as well as to increase participant satisfaction;
4. To improve the accuracy, accessibility and utilization of BLSA data stored in the computer-based data bank; and
5. To facilitate the use of the data from the BLSA by all investigators through consultation and assistance on statistical and computer methodology.

To accomplish its research mission, the LSB is organized into three functional units: Participant Scheduling and Testing, concerned with coordinating all and performing some of the testing during the two and one-half day visit of each participant; Data Management, concerned with entry, storage, and utilization of BLSA data and computer support of all research and administrative activities of the LSB; and, Statistical Sciences, concerned with the direction and conduct of data analyses, the development and application of statistical theory and methodology and consultation. Every person on the LSB staff has responsibilities related to both the research and administrative functions of the Branch. Participant retention, recruitment and other related functions cross organizational lines and are coordinated through working groups and committees established by the Chief, LSB.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00015-29 LSB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Baltimore Longitudinal Study of Human Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

J. L. Fozard

Chief

LSB, NIA

## COOPERATING UNITS (if any)

Other Investigators: See next page.

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

14.75

## PROFESSIONAL

3.80

## OTHER:

10.95

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The Baltimore Longitudinal Study of Aging (BLSA) is a major research resource for scientists doing work in the field of Gerontology. It provides a well-described group of men and women between 20 and 96 years of age for studies of the mechanisms of human aging. Currently some 50 projects in physiology, biochemistry, psychology, nutrition, pharmacology, endocrinology, and genetics, are in progress, being carried out by intramural scientists in 11 sections of 8 different laboratories.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00241-05 LSB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders)

Development of Statistical Methodology for the Analysis of BLSA Data

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Larry J. Brant

Mathematical Statistician

CPB NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Longitudinal Studies Branch

## SECTION

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL

0.7

## OTHER

0.3

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The theoretical development of statistical methodology is progressing in the areas of epidemiological models, multiple comparisons, survival analysis, and the design of experiments, each of which is applicable to longitudinal studies. The research utilizes various regression methods for prospective studies, Bayesian theory in conjunction with decision theory, and numerical computing methods. The methodology created provides original contributions to experimental testing associated with longitudinal studies, the simultaneous comparison of specified effects (e.g. treatments against a control or placebo), epidemiological study of disease states, survival or failure analysis of longitudinal data and other longitudinal observations representing growth, physical and mental disability, and other physical changes in humans and animals. The emphasis of this research is on the development of methods which yield cogent yet easily understood results when applied to data. The creative use of Bayesian theory in the area of multiple comparisons will fill a void in the established statistical armamentarium.



# ANNUAL REPORT OF THE LABORATORY OF BEHAVIORAL SCIENCES

## NATIONAL INSTITUTE ON AGING

### I. SIGNIFICANT ADMINISTRATIVE EVENTS

There were two major administrative events in FY87: First was the successful recruitment of Dr. David E. Anderson to be Chief of the Behavioral Medicine Section (BMS); and second was the conversion of Dr. Mark I. Talan from Visiting Scientist to Medical Officer. Dr. Anderson is an expert in hypertension research. He has developed an innovative animal model (dog) that has provided striking evidence for the interaction between behavioral and metabolic (salt) factors in the mediation of high blood pressure. His research in LBS will focus on clinical studies of behavioral regulation of physiological adaptations of patients to their natural environments. However, he also will continue his research on the interaction between behavioral and metabolic factors in hypertension in collaboration with scientists in the Behavioral Physiology Section (BPS). Dr. Talan's conversion to permanent staff is a major development in the consolidation of the programs of BMS and BPS. The assurance of his continued presence in LBS will guarantee the continuation of his important studies of thermoregulation and will increase the interaction between the basic science programs of BPS and the clinical programs of BMS. Some examples of this interaction are noted below.

### II. SCIENTIFIC ACCOMPLISHMENTS

#### A. Behavioral Medicine Section

There are four, active programs in BMS and each has a number of ongoing clinical projects.

1. The pulmonary program is studying of the role of chest wall muscles in breathing. The accumulation of data on a cross-sectional, normative sample of subjects to a standardized, 8 min. abdominal breathing task is nearing completion. To date, 80 subjects between the ages of 21 yrs. and 60 yrs. have been studied; and 24 of a projected cohort of 40 subjects between the ages of 61 and 80+ yrs. have been tested. These data will provide the bases for a variety of comparative studies of patients with various pulmonary or cardiovascular disorders, or normal subjects with specialized characteristics. For example, a study of professional opera singers has shown that these subjects respond to the breathing task with significantly less cardiovascular work than does their peers ~~who were selected from the normative group~~ to be matched for age, sex, smoking history and exercise history.
2. The hypertension program is evaluating the clinical effectiveness of a BEHAVIORAL STEPPED CARE program for the control of high blood pressure. One study which investigated the roles of self-monitoring of blood pressure, self-administered systolic blood pressure biofeedback and self-administered relaxation in blood pressure control has been completed. A second, pilot study testing the BEHAVIORAL STEPPED CARE program in the control of isolated systolic hypertension (ISH), is nearing completion. The first study followed a cohort of 103 patients (51 experimental and 52 controls) for about 2 yrs/patient. The





experimental group was entered into the BEHAVIORAL STEPPED CARE program and the control group was followed and evaluated regularly but remained under the care of their regular physicians. The major findings are that 49% of the stepped care patients either reduced (12%) or eliminated totally (37%) their anti-hypertensive medications whereas only 24% of the referred care patients reduced (18%) or eliminated totally (6%) their medications. The major benefits were achieved by patients who were initially taking diuretics or beta-blockers. The decrease in medication needs also was associated with a decrease in costs: \$38/yr/patient among the diuretic-treated patients in the stepped care group vs. an increase of \$100/yr/patient in the referred care group; \$60/yr/patient in the beta-blocker group vs. \$27/yr/patient in the referred care patients; \$33/yr/patient in the group taking vasodilators vs. an increase of \$24/yr/patient in the control group. Overall, the stepped care patients had a reduction of \$44/yr/patient whereas the control group had an increase of \$32/yr/patient for an overall group difference of \$76/yr/patient. It also is important to note that these differences in medication requirements and costs occurred without any change in average blood pressure. The study of ISH is sufficiently near completion to show that these patients are able to benefit significantly from BEHAVIORAL STEPPED CARE therapy: the average fall in blood pressure is about 10/4 mm Hg. over seven months.

3. The outpatient continence treatment research program has been an outstanding success: The clinical findings have been impressive, and the proliferation of continence treatment clinics patterned after ours throughout the nation and in Europe has been gratifying. Dr. K. Burgio, a Senior Staff Fellow in LBS for the last six years who has had primary responsibility for carrying out this research program, has accepted an appointment as Assistant Professor in the Department of Medicine at the University of Pittsburgh. When she leaves, this laboratory will be closed so this is a final report. A recently completed study of a group of 20 men (aged 55 to 87 yrs.) with urinary incontinence following prostate surgery has shown that: 1) A two hr. voiding schedule resulted in a 33% average increase in the frequency of urge incontinence and a 28% average decrease in the frequency of stress incontinence; 2) following one to five biofeedback training sessions, patients with: a) urge incontinence showed an 81% average reduction of incontinence; b) stress incontinence showed a 78% reduction; c) continual leakage showed only a 17% improvement. Interestingly, it was possible to successfully treat urge and/or stress incontinence in a patient even though his continual leakage was unchanged. Although our treatment procedure is very efficient and cost-effective since most patients are successfully treated with a few training sessions, we still are studying ways to improve treatment. One study compared biofeedback with a behavioral training program without feedback. This program was administered by a nurse-practitioner (another cost savings innovation) in a geriatric, outpatient service. Seven of the patients had stress incontinence and 20 had urge incontinence. About half in each diagnostic group received feedback and the other half received non-feedback training only. The non-feedback group achieved a mean reduction in incontinent episodes of 82% whereas the feedback group had an average of 79% improvement. An ongoing study designed to compare bladder/anorectal feedback with vaginal muscle feedback in stress incontinent women is showing that among eight patients who received vaginal muscle feedback there was an 80% reduction in incontinence whereas among seven patients in the bladder/anorectal group there was a 90%



improvement. This study is only about half completed. Three studies are looking at the epidemiology and demography of incontinence and toileting behavior. One study surveyed a cohort of 232 premenopausal women in the greater Pittsburgh area (The Healthy Women Study) and found that the self-reported prevalence of involuntary urine loss is 53%; 34% reported that the incidence was at least one/month and 11% reported daily urine loss; pure stress incontinence was most common (54%), urge incontinence was least common (11%), and mixed stress and urge incontinence was present in 35% of the incontinent subjects; in 72% volume loss was only one or two drops, and only 36% wore protection; finally, it is noteworthy that only 24% sought treatment for incontinence. The Baltimore Longitudinal Study of Aging (BLSA) has provided data on the daily (6:00 AM through midnight) voiding behavior of 413 men and 244 women across the age spectrum. Preliminary analyses have shown that the overall mean frequency of voids is 6.2/day with a range of 5.4 (40 - 50 yr. old men) to 7.2 (30 - 40 yr. old women). We also examined the influence of frequency and independence of toileting, mental status and toileting skills including mobility in 24 continent and 18 incontinent clients in a medical, adult day care facility. Incontinent clients had significantly lower mental status, used the toilet less often and required staff assistance more often. In addition, all of the continent but only 46% of the incontinent clients were able to self-toilet (even with verbal and physical guidance), and the incontinent clients who were able to self-toilet required significantly more time to do so. A project designed to study the relationship between the amplitudes of the external anal sphincter and the external urinary sphincter responses is showing a monotonic relationship between the two sphincters; furthermore, this relationship is not affected by the degree of bladder fullness. Since mobility impairment is a common concomitant of incontinence, we also examined a behavioral strategy for improving mobility in the day care setting. A strategy combining wheelchair restriction and prompts for walking was effective in increasing mobility in three elderly (71 - 83 yrs.) clients who used their wheelchairs more than necessary. Average baseline, non-wheelchair mobility was 13 ft/day; following treatment mobility increased to an average of 290 ft/day.

Although it was not done in LBS, one other study is relevant here. In 1985 we trained a group of French geriatricians to apply our biofeedback techniques in the treatment of incontinent elderly patients. Recently, this group reported their experiences in treating elderly patients in a rehabilitation service: They studied 49 women (mean age 84.6 years) and 8 men (mean age 78.5 years) with either stress, urge or mixed incontinence. The patients' mental status ranged from severe dementia to normal cognitive function; about 60% required treatment for depression; and about 30% were unable to dress or undress. Among the 37 patients who completed treatment: 10 (27%) were not improved; 5 (13%) were improved (an average of 68% reduction in frequency of accidents); and 22 (60%) were rated as cured. Since improvement was based on direct observations of wetness or dryness on the rehabilitation unit, these data are quite impressive. It is noteworthy that these patients required considerably more intense training (daily sessions for about four weeks) than do our outpatients (1 - 5 sessions). However, the high success rate justifies the intervention, and these investigators report that the application of biofeedback for urinary incontinence is expanding in France.

4. The inpatient geriatric continence program is a major research effort co-sponsored by NIA and the Health Care Financing Administration (HCFA). Not





only is this program providing results on the management of incontinence in a long-term care setting, but also it is generating a number of cognate findings of general interest to long-term care providers. The overall finding from the program is that 22 of 31 (71%) patients were drier after discharge from the Continence Unit; 65% were drier on their home units within the first month after discharge and 59% were drier at three month follow-up. Since this program is still active, these must be considered as preliminary data. Two, special interventions are being studied on the continence unit; one for the treatment of urinary incontinence and one for the treatment of fecal incontinence. An experimental analysis of the bell-and-pad procedure for treating urinary incontinence is nearing completion. The bell-and-pad procedure was originally developed to manage enuresis in children and has been successfully applied to mentally retarded children as well but has not been adequately tested on long-term care, geriatric patients. The procedure uses a specially designed pad which closes a battery-operated electrical circuit whenever the pad is wet; and the circuit sounds an alarm. We are finding that cognitively impaired, immobile patients can be taught to increase dryness using this tool. Further studies suggest that through the use of a behavioral strategy called fading (systematic, gradual withdrawal of the bell cue), the bell-and-pad alarm system can be discontinued and the patient will retain a level of dryness. Our study of fecal incontinence couples dietary control (bran) with behavioral control (prompted toileting). Although no treatment data are yet available, it is noteworthy that we have developed a reliable and valid scale for measuring stool quality. This tool should have wide application since there is no other comparable instrument available despite the widespread prevalence of diarrhea and constipation. We also are examining the cost-effectiveness of our treatments. A analysis based the first 17 patients discharged from the unit shows a reduction in cost following treatment. Prior to admission the Medicaid daily reimbursement for these patients was \$345/day; after discharge from our unit, the cost had been reduced to \$330/day. Overall, 24% of the patients went down one level of care, and 12% went up one level of care. Thus, the savings for HCFA was \$15/day (\$0.90/patient/day). We are now negotiating a contract with HCFA to investigate this cost savings in further detail. Last year we reported a general survey of the institution that revealed that 82% of the residents were incontinent, and that mobility impairment was a more frequent concomitant of incontinence than was cognitive impairment. Further analyses have shown that the incontinent patients relative to continent patients are: more dependent on the staff to toilet them but are not reliably toileted; more likely to show deficits in their activities of daily living, have lower general activity levels and are more likely to engage in stereotypic behaviors; more likely to receive laxatives. (there are no other medication differences); and are less likely to have urinary tract infections, be hemiplegic or to have a history of strokes.

As noted above, this program has spawned a number of interesting, cognate projects. These can be broadly classified into two areas, assessment of aberrant behaviors and attitudes about treatment of elderly persons. One study examined the effect of antipsychotic drugs on behavior, and a second compared continuous administration of major tranquilizers with "PRN" administration in a community and a teaching nursing home. Patients currently taking antipsychotic medications showed a number of aberrant behaviors such as noncompliance, acting-out, aggression, verbal abuse, disruption and feeding problems. They also showed a paradoxical effect of sleeping more, but of having an unusually high activity level when awake. About 20% of the patients in the two nursing



homes had prescriptions for major tranquilizers. Since about 60% of the PRN medications were never given during the three month study period, and 23% were administered no more than once/month, the prn prescriptions produced a much lower drug burden on the patients than did the continuous administration prescriptions. Documentation of drug effectiveness was poor, albeit more likely to exist for prn administration. Among the many possible risk factors associated with major tranquilizer administration, only wheelchair or assistive device dependency was a useful predictor of prescriptive practices: patients needing such aids were more likely to be given prn medication. A survey of nurses indicated that behavior problems of their patients are among their major concerns; that they felt they had not been adequately prepared to deal with these problems; that they were uncertain about the efficacy of psychotropic medications to manage such problems; and that they regarded behavioral procedures as effective and acceptable means for dealing with problem behaviors. Finally, a survey of attitudes toward behavioral procedures among college student revealed that they expressed different views about the same procedure when it was used with an elderly client than when it was applied to a child. In particular, some of the more effective methods for managing aberrant behaviors were judged to be more active when applied to elderly clients than when applied to children.

## B. Behavioral Physiology Section

The scientific principle that underlies all of the research in LBS is that all neurally mediated responses are behavior. Thus, any attempt to understand physiological function of neurally mediated responses must identify behavioral as well as physiological mechanisms. Research in the Behavioral Medicine Section applies this principle to the assessment and treatment of patients; research in the Behavioral Physiology Section is designed to identify and characterize the relevant physiological and behavioral mechanisms.

1. Exercise is a ubiquitous behavior, the understanding of which requires the integration of physiological as well as behavioral concepts. BPS has developed an animal model for analyzing this interaction. Nonhuman primates are trained to exercise (repeatedly lift weights) and to slow their heart rates. Once an animal is trained to emit both behaviors, it is required to combine these skills, and studies are then carried out to identify the underlying mechanisms. Ongoing studies which are looking at the autonomic mechanisms mediating the control of the circulation are showing that the animal does not learn a specific neural pathway to control its heart during exercise; rather it learns the skill and then utilizes whatever pathway is available. Our studies indicate that neither vagal blockade nor sympathetic blockade prevents the animal from slowing its heart while exercising. However, in order to manage this behavior, the animal must modulate other control mechanisms. For example, under control conditions, when the animal is slowing its heart it is very efficient since the exercise is accomplished without any change in V02. Thus, the animal is able to supply more blood to working muscles. However, when any branch of the autonomic nervous system is blocked, V02 increases significantly more during the combined condition. Thus, the evidence points to an intimate integration and regulation of physiological adjustments to behavioral demands in which the behavioral contingencies define the physiological requirements. Normally, the animal expends more cardiovascular work than is necessary to maintain the task; when it is trained to slow its heart, it becomes more efficient, reducing its cardiovascular work while maintaining the physical





work; however, once its capacity to modulate its autonomic nervous system is reduced, it can only maintain the task by increasing the work of the circulation and reducing its efficiency.

2. A major research effort is going on in the nonhuman primate laboratory to examine diurnal changes in hemodynamic patterns. A study finished this year has shown that cardiac output falls steadily throughout the night, and that peripheral resistance rises in order to maintain blood pressure. The fall in cardiac output is mediated by a fall in heart rate since stroke volume does not change. Ongoing studies indicate that neither beta-blockade nor alpha-blockade nor total sympathetic blockade changes this basic, neurally-mediated pattern. Since this is so, other vasomotor regulators such as vasopressin or angiotensin must play a role. Nevertheless, the fact that sympathetic blockade does not prevent this diurnal pattern, suggests that blood volume redistribution may not be the mechanism underlying these changes. Since the only other mechanism which could occur would be a reduction in total blood volume, these findings suggest that the water volume in the blood may fall throughout the night. One intriguing hypothesis suggested by this inference is that as water volume falls, the concentration of protein bound substances in the blood rises. If this is true, then it means that many of the long-acting drugs now in use, many of which bind to hemoglobin and other proteins in the blood, may also increase in concentration throughout the night. Studies to test this hypothesis in specific patient groups are now beginning.

3. Thermoregulation, like exercise and diurnal rhythmicity is a neurally-mediated pattern of physiological and behavioral adjustments to the environment. Several studies over the past year in BPS have shown that behavioral conditioning (viz, experience) as well as physiological changes regulate the ability of mice to improve their body temperature responses to repeated exposures to cold -- ie, they show habituation. Furthermore, if habituated animals are not regularly exposed to cold, they will dishabituate. Previous research in BPS showed that electrical stimulation of the brain in a "rewarding" site -- ie, the animal will press a bar to obtain stimulation to its brain -- will prevent dishabituation. Studies done this year show that this effect can be learned! Animals which merely are allowed to spend time in the chamber in which they received rewarding brain stimulation weeks earlier also will show dishabituation. Studies are now planned to identify the physiological mechanisms mediating this effect. These studies will examine the role of brown adipose tissue (BAT) in this effect and will be carried out by an IRTA fellow. Evidence for the importance of BAT in thermoregulation comes from a number of sources. One study carried out in the past year in BPS has shown that adult mice that have their interscapular BAT removed fail to habituate to repeated cold exposure. Since old animals also fail to habituate to repeated cold exposure and since they appear to have reduced amounts of interscapular BAT, this finding suggests that BAT may play a role in the age-related decline in cold tolerance. Cold tolerance not only is related to the ability of an animal to respond to a cold challenge, but also is related to the resting body temperature of the animal. Old animals not only show poor habituation but also have lower body temperature than do adult animals. Studies this year have examined age differences in metabolic function to better understand the mechanism of reduced body temperature in older animals. Analyses of a number of metabolic parameters indicate that change in  $\dot{V}O_2$  during a three hour cold stress is biphasic. Within the first five minutes  $\dot{V}O_2$  rises and then for the remainder of the interval it falls. Research this year has shown that the



initial rise in  $\dot{V}O_2$  is only about 1/2 as great for old animals as it is for adult animals; furthermore, the subsequent decline in  $\dot{V}O_2$  is twice as great for the old animals as the adult mice. The respiratory exchange ratio ( $\text{CO}_2$  production/ $\text{O}_2$  consumption) was the metabolic parameter which best differentiated the adult animals from the old ones during the first five minutes. These data suggest strongly that the rapid adjustment to a cold stress may be a critical age variable. Investigators in BPS have been collaborating with investigators in LCMB to study the physiology of embryonic hypothalamic brain grafts. Our group has been looking at thermoregulation in old animals as a means of evaluating the functional significance of such grafts. Ongoing studies are showing that old animals which receive such grafts show a significant rise in body temperature. Continuing studies will pursue this promising finding.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00063-19 LBS

## PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Learned Modification of Visceral Functions in Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

Mark I. Talan, M.D., Ph.D.

Medical Officer

LBS, GRC, NIA

## COOPERATING UNITS (if any)

Laboratory of Cellular and Molecular Biology  
University of California, San Diego Medical School

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine

## INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

## TOTAL MAN-YEARS:

5.58

## PROFESSIONAL:

1.83

## OTHER:

3.75

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The purpose of this project is to investigate the role of the central nervous system in behavior. In some experiments we are studying the extent to which the cardiovascular system can be modified by instrumental conditioning. In other experiments we are examining age-related changes in thermoregulation. In other experiments we are examining diurnal patterns of hemodynamic performance.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00067-19 LBS

## PERIOD COVERED

October 1, 1986 through September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Learned Modification of Visceral Function in Man

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.	Chief, LBS	LBS, GRC, NIA
Kathleen A. McCormick, R.N., Ph.D.	Research Nurse	LBS, GRC, NIA
Kathryn L. Burgio, Ph.D.	Sr. Staff Fellow	LBS, GRC, NIA
Michael S. Glasgow, Ph.D.	Research Physiologist	LBS, GRC, NIA

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center; CareFirst Medical Plan; New York City Opera Company; Wolf Trap Farms; University of Pittsburgh School of Medicine; BLSA

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine

## INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

## TOTAL MAN-YEARS:

4.96

## PROFESSIONAL:

2.56

## OTHER:

2.4

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project is concerned with the application of behavioral methods and principles to clinical medicine. Subjects are patients selected from various medical clinics, or normal subjects who are studied to evaluate potential clinical methods. The main focus of this project is on clinical problems especially relevant to middle aged or elderly persons.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00071-01 LBS

## PERIOD COVERED

October 1, 1986 through September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Isolated Systolic Hypertension

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine

## INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.15

## PROFESSIONAL:

.05

## OTHER:

.10

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Isolated systolic hypertension is a common problem among elderly persons. This project is designed as a pilot study to estimate the clinical effectiveness of a behavioral stepped-care program to lower systolic pressure in these patients.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG00072-02 LBS

## PERIOD COVERED

October 1, 1986 through September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Behavioral Assessment and Treatment of Incontinence in Nursing Home Residents

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bernard T. Engel, Ph.D.

Chief, LBS

LBS, GRC, NIA

Kathleen A. McCormick, R.N., Ph.D.

Research Nurse

LBS, GRC, NIA

Louis Burgio, Ph.D.

Psychologist

LBS, GRC, NIA

Frieda Butler, R.N., Ph.D.

IPA Fellow

LBS, GRC, NIA

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center; Health Care Financing Administration; Office of the Surgeon General of the United States

## LAB/BRANCH

Laboratory of Behavioral Sciences

## SECTION

Behavioral Medicine

## INSTITUTE AND LOCATION

National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

## TOTAL MAN-YEARS:

4.06

## PROFESSIONAL:

3.06

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Incontinence is a major reason for institutionalizing elderly persons, and is widespread in nursing homes. This project is designed to evaluate behavioral intervention techniques for the treatment of these patients.



# Annual Report of the Laboratory of Biological Chemistry

## National Institute on Aging

1. The loss with age of bone mineral from rat femurs, measured by single photon absorptiometry. Single photon absorptiometry was used to examine the changes in cortical and trabecular bone mineral content in excised femurs from young adult (6 mo), mature adult (12 mo) and senescent (24 mo) male and female animals. Bone mineral content of the femur distal metaphysis, representing trabecular bone, decreased markedly in the aged rat. Bone mineral content of the femur midshaft, representing cortical bone, increased progressively with advancing age. The width of the femur at the scan site also increased with age. Normalizing the midshaft bone mineral content by width partially compensated for the age-associated increase. However, when bone mineral values were normalized by the cortical area at the scan site, to take into account the geometric differences in the femurs of different aged animals, maximum bone densities were found in the mature adult and these values decreased slightly in the femurs from senescent rats. These findings indicated that in the rat femur bone mineral loss with age was site-specific.

2. Bone status of the aging female rat. The bone status of female rats, 6, 12 and 24 mo of age was examined. Diaphyseal Ca, Pi and osteocalcin did not change significantly with increasing age. Serum Ca and Pi concentrations were not altered in the aged rat. Immunoreactive PTH levels increased significantly with age. Serum osteocalcin decreased progressively from 6 to 12 mo (-21%) and from 12 to 24 mo (-23%). Maximum breaking force required to fracture femurs at midshaft did not change with senescence. Hence, the strength of the femur as an intact organ was not compromised in aging. However, ultimate stress, a parameter which normalizes for differences in bone geometry and size, decreased 14% from 12 to 24 mo. Changes in other biomechanical parameters, including yield and ultimate deformation, strain and modulus of elasticity, were relatively small. Morphometric measurements indicated a progressive age-related increase in second moment of area and cortical area. Medullary area did not change with age. Therefore, strength of the intact femur was maintained by architectural compensations, although normalized tissue strength decreased in senescence. The results indicate that bone status and mineral metabolism was compromised in the aged female rat, but to a less degree than found for the senescent male rat. In addition, the present findings indicate that the changes in bone and mineral metabolism in the aged female rat differed from the alterations previously reported in the ovariectomized young adult. Thus, if the two models could be compared, we would suggest that age-related changes in levels of circulating female hormones per se did not account for the bone changes found in the aged female rat.





3. Mineral homeostasis and skeletal histology in the aged female rat. Tibial histomorphometry of female rats at age 2, 6, 12, 18 and 24 mo was examined in conjunction with serum indices of mineral homeostasis. The serum Ca, BUN, creatinine and 25-(OH) vit. D<sub>3</sub> levels did not change. Serum P fell from 2.33±0.41 to 1.44±0.26 mM. 1,25-(OH)<sub>2</sub> vit. D<sub>3</sub> declined from 51±3 to 36±3 pg/ml. The PTH concentration remained normal 21±2 pM until 18 mo (29±4) and then rose dramatically at 24 mo (49±9). The calcitonin levels showed a progressive rise throughout the life span of the animal, from 55±15 to 530±94 pg/ml. Bone volume fell from 20.2±1.1% to 10.4±1.0% by 12 mo and continued to fall to 4.2±1.0% at 24 mo. Bone formation including osteoid volume, osteoblastic surface, tetracycline surface and mineralization rate decreased 97%, 91%, 100% and 100% from 12 to 24 mo. Osteoclast number transiently fell at 6 mo to 1.0±0.6 per mm and rose abruptly at 18 mo to peak at 7.8±1.1 by 24 mo. These results suggest that, with age, serum Ca was maintained despite falling 1,25(OH)<sub>2</sub>D<sub>3</sub> levels by increasing PTH secretion. At the skeletal level, osteoblast insufficiency preceded increases in osteoclast bone resorption, resulting in osteopenia.

4. Characterization of the human osteosarcoma cell line (CRL-1427) as a model osteoblast-like human bone cell. CRL-1427 cells, a rapidly growing and readily cultured human bone cell line, was found to possess PTH-sensitive adenylate cyclase, 1,25(OH)<sub>2</sub>vit.D<sub>3</sub>-induced osteocalcin synthesis and alkaline phosphatase activity. The cells did not respond to calcitonin. These results indicate that the cells were osteoblast-like and, thus, might serve as a cell model for human osteoblasts.

5. Regulation of bone resorption by a phenylalkylamine-sensitive calcium channel. Phenylalkylamine receptor binding sites were demonstrated in osteoblast-like osteosarcoma cells and dissociated human osteoblasts using (-)[<sup>3</sup>H]desmethoxyverapamil. These bindings sites corresponded to a novel osteoblast calcium channel demonstrated by patch clamp analysis. Parathyroid hormone stimulated calcium influx into osteosarcoma cells and parathyroid hormone induced *in vitro* bone resorption were blocked by phenylalkylamines with potencies and selectivity suggesting an association with the (-)[<sup>3</sup>H]desmethoxyverapamil labeled binding sites. Conceivably, phenylalkylamines and related drugs may be useful in the treatment of osteoporosis and other conditions involving excessive bone resorption.

6. Biochemical mechanism of the age-associated decrease in vitamin D-sensitive intestinal calcium absorption. Last year we reported the decreased calcium uptake in duodenal cells from senescent rats and the decreased capacity of renal mitochondria from aged animals to synthesize 1,25(OH)<sub>2</sub>D<sub>3</sub>, the active hormonal form of vitamin D. This year, we found that the serum concentration of 1,25(OH)<sub>2</sub>D<sub>3</sub> in 24 mo male rats was 40% less than in 6 mo animals, 26±2 pg/ml compared to 43±4 pg/ml (p<0.01). Serum levels of 25-(OH)D<sub>3</sub> did not differ significantly, 16±2 ng/ml vs 17±2 ng/ml for 24 and 6 mo male rats, respectively. In addition, we discovered that the total number of 1,25(OH)<sub>2</sub>D<sub>3</sub> receptors and number of receptors occupied by the hormone in intestinal cells were decreased in cells from aged (24 mo) rats compared to cells from young adults (6 mo). The affinity of the receptor for the seco-steroid was not altered in aging. Calcium binding protein, a major gene product of vitamin D induction, was decreased by half in cells from aged animals (see Table).



**Effect of Age on Calcium Uptake in Intestine,  
1,25(OH)<sub>2</sub>D<sub>3</sub> Receptor and Calcium Binding Protein.**

**1,25(OH)<sub>2</sub>D<sub>3</sub> Receptor**

Age (mo)	Ca Uptake (nmol/mg cell prot·min)	Total (fmol/ mg prot)	Occupied (fmol/ mg prot)	Unoccupied (fmol/ mg prot)	Kd (nM)	CaBP (nmol/ mg prot)
6	5.2 ± 0.7	566 ± 18	121 ± 12	444 ± 19	0.15 ± 0.01	1.7 ± 0.2
24	2.9 ± 0.4	444 ± 22	69 ± 7	375 ± 18	0.17 ± 0.02	0.8 ± 0.1
	p < 0.01	p < 0.01	p < 0.01	p < 0.10	N.S.*	p < 0.01

\* Not Significant

**7. Desensitization to PTH in Renal Cells from Aged Rats is Associated with a Decrease in PTH Receptor Binding Sites.** Last year we reported that renal cells from aged (24 mo) vs mature (6 mo) rats had decreased PTH-responsive Na-Ca exchange, PTH-induced cAMP production and PTH-stimulated adenylate cyclase activity. In addition, we found that the blunting of the responses to PTH was associated with decreased cholera toxin-mediated ADP-ribosylation of the  $\alpha$ -subunit of the stimulatory GTP-binding protein (Gs) and the pertussis toxin-mediated ADP-ribosylation of the inhibitory GTP-binding protein (Gi). This year, we found that the desensitization to PTH was also associated with a decrease in PTH-specific receptor binding sites on the basolateral segment of the renal cell plasma membrane. Using the synthetic analog <sup>125</sup>I- [Me<sup>8</sup>, Me<sup>18</sup>, Tyr<sup>34</sup>] PTH (1-34) amide as the PTH probe, Scatchard analysis revealed that the Bmax decreased from 92.1±9.3 fmol/mg protein in membranes from 6 mo rats to 36.7±6.1 in membranes from 24 mo animals. The affinity of the receptor for the hormone (Kd) did not change with age, being 1.36±0.12x10<sup>-9</sup>M and 1.25±0.2x10<sup>-9</sup> for 6 and 24 mo rats, respectively.

**8. Desensitization to PTH in Renal Cells from Aged Rats Can Be Reversed by Parathyroidectomy of the Senescent Animal.** The aged (24 mo) rat exhibits blunted renal responses to PTH, including Na-Ca exchange, adenylate cyclase activity, number of PTH receptor binding sites and GTP-binding protein (Gs and Gi) function. The aged rat also has an elevated level of serum iPTH (mid-molecule immunoassay). When the aged rat was parathyroidectomized for 48 to 72 hr, the losses in PTH responsiveness, measured by Ca transport and adenylate cyclase were completely restored. The loss of PTH receptors and the decrements in cholera toxin- and pertussis toxin-mediated ADP ribosylation were partially reversed. These findings indicate that the age-associated blunting in the responses of renal cells to PTH can be reversed at least in part, by removal of the parathyroid gland and suggest the therapeutic potential of PTH receptor blocking agents in hyperparathyroid conditions.



**9. Preparation of cDNAs for Gs, Gi, Go and actin.** Because we found decreased levels of GTP-binding proteins, Gs and Gi, in the kidney of aged rats, we are testing the hypothesis that the syntheses of these signal transducing proteins decline in the aged rat. Therefore, labelled cDNAs for Gs, Gi, Go and actin were prepared for future quantitation of the respective mRNAs.

**10. Pertussis Toxin Blocks the Action of  $\alpha_2$ -Adrenergic Hormones in Blunting the Response of Renal Cells to PTH.** Last year, we reported that a cultured cell line from opossum kidney (OK cells) had  $\alpha_2$ -adrenergic receptors and that epinephrine, acting as an  $\alpha_2$ -adrenergic agonist, inhibited the actions of PTH in enhancing cAMP formation and in inhibiting phosphate uptake. When the cells were pretreated with pertussis toxin, PTH-generated cAMP increased from  $37 \pm 7$  to  $87 \pm 9$  pmol/dish, suggesting that Gi modulates PTH-induced cAMP formation. In addition, pertussis toxin completely blocked the inhibitory action of epinephrine on the PTH-induced increase in cAMP. This finding suggests that the action of  $\alpha_2$ -adrenergic hormones in renal cells is mediated via the Gi GTP-binding protein.

**11. PTH Regulation of Cytosolic  $\text{Ca}^{2+}$  in Proximal Tubules.** Last year, we reported that PTH increased cytosolic  $\text{Ca}^{2+}$  in rat renal proximal tubules by a mechanism involving phospholipase C-stimulated hydrolysis of polyphosphoinositides, but independent of cAMP. In continuing studies, we found that pretreatment of the tubules with the  $\text{Ca}^{2+}$  ionophore, ionomycin, depleted the intracellular pool of  $\text{Ca}^{2+}$  and prevented the rise in  $[\text{Ca}^{2+}]_i$  when the tubules were subsequently exposed to PTH. Pretreatment of the tubules with verapamil or  $\text{LaCl}_3$  had little effect on the PTH-induced transient increase in  $[\text{Ca}^{2+}]_i$ , further suggesting a minor role of extracellular  $\text{Ca}^{2+}$  in this action of PTH. Increases in  $[\text{Ca}^{2+}]_i$  by 40 nM rPTH (1-34) was antagonized by bPTH (3-34) and bPTH (7-34), with 50% inhibition found with 80 nM and 5  $\mu\text{M}$ , respectively.

**12. The PTH-Induced Increase in Cytosolic  $\text{Ca}^{2+}$  is Desensitized by PTH.**

Pretreatment of tubules with 200 nM rPTH (1-34) for as little as 3 min abolished the normal response to PTH, but had no apparent effect on the ability of norepinephrine or angiotensin II, at maximal concentrations, to increase  $[\text{Ca}^{2+}]_i$ . The extent of desensitization was dependent on the concentration of rPTH (1-34), was not produced by rPTH (3-34) either alone or in combination with dibutyrylcAMP, but was attenuated by exposure to rPTH (3-34) prior to rPTH (1-34).

**13. The PTH-Induced Increase in cAMP in OK Cells is Desensitized by PTH.**

Preliminary studies demonstrated that preincubation of OK cells with PTH desensitized the cells, causing the cells to produce less cAMP when subsequently treated with PTH. The magnitude of desensitization was dependent on the concentration of PTH in the preincubation medium and the time of preincubation.





14. The Concentration of Ionized Ca in Serum is Unaltered in the Aged Male Rat. The concentrations of  $\text{Ca}^{2+}$  in the sera of 6 mo and 24 mo male rats were  $1.23 \pm 0.02$  and  $1.19 \pm 0.02$  mM, respectively. Total serum Ca also did not change significantly with age, being  $2.19 \pm 0.02$  and  $2.33 \pm 0.04$  mM for 6 and 24 mo animals, in agreement with earlier findings. These results reveal that in the aged rat there is an increased level of serum iPTH (midmolecule), despite the fact that serum ionized  $\text{Ca}^{2+}$  concentration is maintained.

15. Regulation of PTH-Independent Phosphate Uptake in Cultured Renal Cells (OK Cells) by Calcium. Previous studies, *in vivo* and with relatively intact preparations, demonstrated that Ca, in the absence of PTH, controlled phosphate transport. The mechanism by which Ca alters this phosphate uptake is unknown. We examined the effect of altering the concentration of intracellular free Ca ( $[\text{Ca}^{2+}]_i$ ) on the uptake of phosphate in cultured opossum kidney (OK) cells which have proximal tubular-like characteristics.  $[\text{Ca}^{2+}]_i$  was determined with the fluorescent indicator INDO-1/AM). Initial rate (15s) of phosphate (0.1 mM) was measured in the presence of extracellular  $\text{Na}^+$  (150 mM). Uptake was almost completely dependent on  $\text{Na}^+$ . In the presence of 1.0 mM extracellular Ca,  $[\text{Ca}^{2+}]_i$  was  $188 \pm 8$  nM and phosphate uptake was  $131 \pm 5$  pmol/mg prot./15s. Changes, both increases and decreases, in  $[\text{Ca}^{2+}]_i$  were effected by different concentrations of the Ca ionophore, ionomycin, and ionomycin plus EGTA in the absence of extracellular Ca, and by varying the times of incubation with these effectors. Deviation from the basal  $[\text{Ca}^{2+}]_i$  resulted in inhibition of phosphate uptake, the magnitude of inhibition correlated with of the extent of change in  $[\text{Ca}^{2+}]_i$ . Under the same conditions,  $\text{Na}^+$  and D-glucose uptakes were unaffected. These finding suggest that  $[\text{Ca}^{2+}]_i$  may specifically regulate phosphate uptake in OK cells by a PTH-independent mechanism.

16. PTH Enhances 25(OH)vit.D<sub>3</sub> 1-Hydroxylase Activity in Renal Cells. 1-Hydroxylase activity in renal cells was enhanced by PTH, in agreement with the known effect of PTH in increasing 1,25(OH)<sub>2</sub>D<sub>3</sub> synthesis in intact tissue preparations. The cultured cell system will serve as the model in examining the mechanism by which the hormone activates the hydroxylase.

17. Effects of Ovariectomy and Estrogen Replacement on Renal Water and Electrolyte Metabolism in Rats. Ovariectomized rats (ex-breeders) with chronic estrogen replacement (3 weeks) demonstrated higher water intake and greater urine output than untreated ovariectomized rats. Estrogen also increased the glomerular filtration rate (GFR) and calcium, phosphate, sodium, and potassium excretion. When the excretions of the different electrolytes were normalized by the GFR, phosphate, sodium, and potassium excretions in estrogen-treated and -untreated animals were not significantly different. Calcium excretion remained greater after estrogen. Plasma calcium and phosphate concentrations were not altered by hormone replacement. Estrogen treatment also significantly increased the kidney size primarily by increasing cortical weight and protein. Brush border membranes isolated from kidney cortices of estrogen-treated and -untreated rats demonstrated the same  $\text{Na}^+/\text{H}^+$  exchange,  $\text{Na}^+$ -dependent phosphate cotransport, and  $\text{Na}^+$ -dependent glucose cotransport activities.

18. Renal  $\text{Na}^+/\text{H}^+$  Exchange Activity in Aged Rats. In a previous study, we reported that 24 mo male rats had a significant loss in  $\text{Na}^+/\text{H}^+$  exchange activity compared to rats 6, 12, or 18 mo of age. This study included all rats



regardless of renal disease and reduced glomerular filtration rate. In the present study in which only rats with little or no renal disease (based upon normal glomerular filtration rate) were used,  $\text{Na}^+\text{-H}^+$  exchange activity did not decrease in the 24 mo group compared to the 6 mo group. We can contrast this finding with results in young rats (less than 12 mo) in which loss of renal mass and decline in glomerular filtration rate resulted in increased  $\text{Na}^+\text{-H}^+$  exchange activity.

19. Investigations of the  $\text{Na}^+\text{-H}^+$  Exchange Mechanism. Investigations of the  $\text{Na}^+\text{-H}^+$  exchange mechanism in renal brush border membranes demonstrated the existence of a new class of high affinity  $\text{Na}^+$  binding sites on the exchanger. The implication of these results and other findings excluding the presence of allosteric  $\text{Na}^+$  sites is that a minimum of 4 exchanger units interact during the initial transport cycle and that subsequent operations of the system involve consecutive as opposed to simultaneous occupation and translocation of the  $\text{Na}^+$  binding sites.

20. Thyroid Hormone Regulation of  $\text{Na}^+\text{-H}^+$  Exchange Activity. We previously reported that  $\text{Na}^+\text{-H}^+$  exchange activity in brush border membranes isolated from the proximal tubules of the kidney increased in response to hyperthyroidism and decreased in response to hypothyroidism. Kinetically, we found that the  $V_{\text{max}}$  of the exchanger changed without changes in apparent affinities. These results are consistent with either a change in the site density or a change in the rate-limiting step for the exchanger. We sought to distinguish between these two models by studying the transient kinetics of the exchanger. Using low temperature ( $0^\circ\text{C}$ ) to resolve the initial time course of  $\text{Na}^+$  uptake, we observed the presence of an early burst phase that was representative of the first turnover of the exchange and proportional to the site density. When we measured the transient kinetics of the exchanger under a variety of conditions, high and low  $\text{Na}^+$  concentration or with and without a pH gradient, the data best fitted a model showing that thyroid hormone changes the rate-limiting step rather than the site density.

21. Effect of L-Triiodothyronine ( $\text{T}_3$ ) on  $\text{Na}^+\text{-H}^+$  Exchange Activity in Cultured Kidney (OK) Cells. To determine whether  $\text{T}_3$  had a direct action on proximal tubular cells or if the alteration in brush border activity was a secondary adaptive response, e.g. change in filtered  $\text{Na}^+$ , we measured  $\text{Na}^+\text{-H}^+$  exchange activity in OK cells cultured for 4 days in DMEM + 10% FCS depleted of thyroid hormone and in cells cultured in the same medium supplemented with  $\text{T}_3$  for 24 hrs prior to determining  $\text{Na}^+$  (10 mM) uptake.  $\text{T}_3$  did not significantly alter cell number, protein and DNA, thus ruling out cellular hyperplasia and hypertrophy. Initial rate (2 min) of amiloride-sensitive  $\text{Na}^+$  uptake represented 80% of total uptake rate.  $\text{T}_3$  had no effect on amiloride-insensitive  $\text{Na}^+$  uptake.  $\text{T}_3$  stimulated amiloride-sensitive uptake in a dose-dependent relationship, maximum increase of about 60% was obtained with  $10^{-7}\text{M}$  and  $\text{E}_{50}$  with  $10^{-9}\text{M}$   $\text{T}_3$ .  $\text{T}_4$  was 30-times less effective. The increase in  $\text{Na}^+$  uptake had a 12 hr lag period, suggesting a requirement for biosynthesis. The cells maintained an elevated rate of exchange for 48 hrs after removal of hormone, suggesting a slow turnover of the active state. These results indicate that thyroid hormone can stimulate  $\text{Na}^+\text{-H}^+$  exchange activity by direct action on tubular cells.



22. Dopamine Increases Cytosolic Calcium in Renal Proximal Tubules. Dopamine caused an increase in cytosolic  $\text{Ca}^{2+}$  comparable to that induced by PTH, with half-maximal stimulation at 3 nM. Pretreatment of tubules with the D-1 receptor antagonist SCH-23390 or the D-2 antagonist spiperone had little or no effect on this dopamine action. The D-1 agonists SKF38393 and SKF8 had no effect by themselves, but antagonized the stimulation by dopamine. The D-2 agonist LY171555 was neither stimulatory nor inhibitory. The  $\alpha$ -antagonist prazosin completely blocked the effect of dopamine. These findings suggest that dopamine elevates cytosolic  $\text{Ca}^{2+}$  by virtue of its weak interaction with  $\alpha$ -adrenergic receptors.

23. Age-Associated Changes in Hormone-Induced Membrane Signal Transduction Systems in Renal Proximal Tubules. The increases in cytosolic  $\text{Ca}^{2+}$  produced by PTH, nor-epinephrine and angiotensin-II were reduced 25 to 35% in tubules from 24 mo compared to 6 mo male rats. However, in 24 mo rats relatively free of kidney disease, assessed by measurement of BUN, the increase induced by PTH was not significantly different from the increase found in 6 mo rats. A negative correlation was observed between response to PTH and BUN. In addition, a positive correlation was observed between responses to PTH and nor-epinephrine. Since both nor-epinephrine and angiotensin-II elicited much larger increases in inositol phosphates than did PTH, along with much larger transients in intracellular free  $\text{Ca}^{2+}$ , the reduced response to PTH observed in some aged rats is not due to an insufficient capacity to generate inositol phosphates and release  $\text{Ca}^{2+}$ , but may be due to diminished signal transduction associated with a reduction in PTH receptors.

24. Signal Transduction Mechanisms in Murine Splenic Lymphocytes. Studies in collaboration with Dr. Nordin, LCP, CIS, showed that Go-T-cells derived from spleens of 6 mo and 24 mo female mice contained similar levels of protein kinase C with a similar, largely cytosolic distribution. Whereas treatment with phorbol myristate acetate caused similar degrees of translocation to a membranous fraction of T-cells from both age groups, exposure to the mitogen Concanavalin A caused half as much translocation in cells from 24 mo compared to 6 mo mice. Studies with the  $\text{Ca}^{2+}$  indicator Indol-1 revealed a similar reduction in mobilization of  $\text{Ca}^{2+}$  from intracellular pools. These data suggest that Go-T cells from old mice have a diminished capacity to transduce a mitogenic signal into increased levels of second messengers, i.e., diacylglycerol and inositol triphosphate, involved in T-cell activation.

25. Bradykinin Induces Changes in Cytosolic Calcium in Human Fibroblasts (IMR-90). Bradykinin, a mitogen in IMR-90 cells, caused a rapid increase in cytosolic  $\text{Ca}^{2+}$  within 1 s after incubation with IMR-90 cells. This was followed by a slower decay in  $\text{Ca}^{++}$  (~ 2 min). A sustained elevated level of  $\text{Ca}^{++}$  was observed for at least 10 min. Bradykinin was effective at a concentration as low as  $10^{-13}\text{M}$ . Prior treatment of the cells with bradykinin prevented any further change in cytosolic  $\text{Ca}^{2+}$  upon a second exposure to bradykinin. Angiotensin II, nor-epinephrine and vasopressin also increased cytosolic  $\text{Ca}^{2+}$ . These data indicate that exposure of IMR-90 cells to different mitogens resulted in rapid and sustained elevation of intracellular free  $\text{Ca}^{2+}$ .





26. Modulation of the  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  Channel in Medullary Thick Ascending Limb Cells.  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels were found in the apical cell membrane of cultured medullary thick ascending limb cells. Because the  $\text{Ca}^{2+}$  site is important in channel regulation, we studied the influence of  $\text{Ca}^{2+}$ , pH and n-bromoacetamide (a protein cleaving agent) on  $\text{K}^+$  channel activity using the excised patch clamp technique. At pH 7.4, 0 mV, the fraction of time spend in the open state,  $f_v$ , was  $\text{Ca}^{2+}$  dependent. Decreasing pH to 5.8 reduced  $f_v$ . The distribution of channel open times showed at least two exponential components with mean open times,  $T_o$ , of 4 and 35 ms. Likewise, the closed times presented at least 3 components with  $T_c$  of 1, 9, and 95 ms at pH 7.4, 0 mV and 5  $\mu\text{M}$   $\text{Ca}^{2+}$ . 1 mM n-bromoacetamide in the bath solution at 2.5  $\mu\text{M}$   $\text{Ca}^{2+}$  reduced the open probability,  $P_o$ , of the channel without affecting single channel conductance. The drug modified channels were still  $\text{Ca}^{2+}$ -sensitive requiring 25 mM  $\text{Ca}^{2+}$  to raise  $P_o$ . Both before and after chemical modification channel openings displayed at least two distributions, indicative of more than one open state. High  $\text{Ca}^{2+}$  (1 mM) protected the channels from modification. We observed a second class of  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels which were normally present in medullary thick ascending limb cells which opened infrequently at 10  $\mu\text{M}$   $\text{Ca}^{2+}$ . We can conclude that: 1. n-bromoacetamide modified the channel by shifting  $\text{Ca}^{2+}$ -sensitivity to very high  $\text{Ca}^{2+}$ ; 2. n-bromoacetamide acted on a site involved in  $\text{Ca}^{2+}$  gating; and 3. a low affinity channel was present in the apical cell membrane with characteristics similar to those of normal channels modified with the drug. These results suggest that the effects of pH and the protein cleaving agent, are at the  $\text{Ca}^{2+}$  binding site and they decrease the  $\text{Ca}^{++}$  affinity of  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  channels in medullary thick ascending limb cells.

27. Mechanism of the Decrease in Renal Ammonia Excretion After an Acid Load in Aged Rats. Last year we reported that the capacity to excrete ammonia into the urine after an acid load was decreased in aged rats. It was not clarified whether this deficiency was due to a decrease in the activity of individual nephrons to produce ammonia or to a decrease in the number of nephrons. Therefore, we examined ammoniagenic activities of individual nephron segments and their responses to an acid load in both young and old rats. We found: (1) blood pH of aged (24 mo) rats (7.34) was lower than that of young (6 mo) rats (7.39) even in a basal state; (2) except for glomeruli, ammoniagenesis in all nephron segments of control aged rats was the same as that of control young rats when compared per length; (3) glomerular ammoniagenesis in aged rats was higher than in young rats, which was significantly related to serum creatinine and BUN levels of the animal; (4) with the same acid load (0.5g  $\text{NH}_4\text{Cl}\cdot\text{kg}$  body  $\text{wt}^{-1}\cdot\text{day}^{-1}$ ), blood pH of young rats was not appreciably decreased (7.34), but that of old rats was decreased severely (7.07). On the other hand, ammoniagenesis of young rats was not significantly increased in any segment; ammoniagenesis was elevated at S1, S2 and DT segments in aged rats; (5) when compared with the same blood pH (7.07), by loading young rats with more acid (1.5g  $\text{NH}_4\text{Cl}\cdot\text{kg}$  body  $\text{wt}^{-1}\cdot\text{day}^{-1}$ ), ammoniagenesis of young rats was dramatically increased in S1, S2, S3 and DT segments, and was significantly higher than in old acidotic rats; (6) when the glutamine  $K_m$  and  $V_{\text{max}}$  for ammoniagenesis in intact S1 segments were compared,  $V_{\text{max}}$  was increased by acidosis in both of young and old rats, but  $K_m$  was decreased only in young rats. These findings demonstrate that the nephron segment in aged rats could respond to the stress of an acid load to produce more ammonia, but the potential activity was lower in aged than in young rats. This decrease in old acidotic rats could be explained in part by a lower affinity to glutamine.





**28. Mechanism of Active  $\text{Ca}^{2+}$  Transport in Skeletal Sarcoplasmic Reticulum.** Kinetic investigations of the enzymatic and transport reactions of the  $\text{Ca}^{2+}$  pump in sarcoplasmic reticulum labelled with fluoro-scein isothiocyanate have uncovered new evidence for the existence of protein subunit interactions in the mechanism of active  $\text{Ca}^{2+}$  translocation. The results suggest that (1) protein subunit interactions occur during active  $\text{Ca}^{2+}$  transport and transport-linked ATP hydrolysis, and (2) these interactions are essential for recycling of the  $\text{Ca}^{2+}$  pump. Although the initial turnover of the pump appears to be unaltered by the removal of these interactions, subsequent activity is greatly diminished suggesting that protein subunit interactions are necessary for the continuous operation of the pump.

**29. Calcium-Induced  $\text{Ca}^{2+}$  Release in Cardiac Sarcoplasmic Reticulum Vesicles.** This year, we continued studies to identify the biochemical changes responsible for the age-dependent decline in active  $\text{Ca}^{2+}$  transport in sarcoplasmic reticulum prepared from rat myocardium. Our studies focused on the mechanism of  $\text{Ca}^{2+}$ -induced  $\text{Ca}^{2+}$  release which is believed to be the primary mechanism for  $\text{Ca}^{2+}$  release leading to the development of contractile force in the heart. Our working hypothesis is that continued release of  $\text{Ca}^{2+}$  triggered by micromolar  $\text{Ca}^{2+}$  in the myoplasm diminishes the amount of net  $\text{Ca}^{2+}$  sequestration in the sarcoplasmic reticulum during relaxation, thereby prolonging contraction duration. Since the rate of  $\text{Ca}^{2+}$  release from the sarcoplasmic reticulum during the onset of contraction shows no age dependence, presumably the  $\text{Ca}^{2+}$  channel density and maximum rate of  $\text{Ca}^{2+}$  flux per channel do not change with age, leaving a delay in channel closing as the most probable cause of the underlying defect. Efforts to characterize the  $\text{Ca}^{2+}$  channel demonstrated that  $\text{Ca}^{2+}$ -activated  $\text{Ca}^{2+}$  release proceeded in 3 distinct phases, the slowest of which accounts for about 75% of the total  $\text{Ca}^{2+}$  efflux and might represent a nonspecific leak. The other two components, that accounted for one-third and two-thirds of the remaining flux, had rates that differ by a factor of five. These presumably correspond to different  $\text{Ca}^{2+}$  selective channels, although their function and origin are unknown. Comparison of the  $\text{Ca}^{2+}$  efflux components in isolated rat cardiac sarcoplasmic reticulum uncovered no age-related differences in their quantitative behavior, suggesting that the decline in  $\text{Ca}^{2+}$  uptake during active (ATP-driven) loading is not due to an increased  $\text{Ca}^{2+}$  leak.

**30. Sarcolemmal membrane  $\text{Ca}^{2+}$  channels.** Two  $\text{Na}^{+}$ -independent  $\text{Ca}^{2+}$  translocation pathways were identified in cardiac sarcolemmal vesicles that exhibited differential sensitivity to inorganic  $\text{Ca}^{2+}$  channel blockers. The pharmacologic and kinetic behavior associated with these pathways suggests that they may be involved in mediation of the transient and slow inward  $\text{Ca}^{2+}$  currents in cardiac muscle.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00051-07 LBC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Regulation of Mineral Metabolism: Pathophysiology of Osteopenia in Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

Bertram Sacktor	Chief, Laboratory of Biological Chemistry	LBC GRC NIA
Bernard A. Bulos	Research Chemist	LBC GRC NIA
Linda Cheng	Research Chemist	LBC GRC NIA
Chuck Filburn	Research Chemist	LBC GRC NIA
C. Tony Liang	Research Chemist	LBC GRC NIA
Sandra Guggino	Senior Staff Fellow (MBS)	LBC GRC NIA
Gary Kiebzak	Senior Staff Fellow (ODD 6/11/87)	LBC GRC NIA
Hirgyuki Hanai	Visiting Fellow	LBC GRC NIA
Daniel Lajeunesse	Visiting Fellow	LBC GRC NIA

COOPERATING UNITS (if any)

M. Levine	Endocrine Division, Department of Medicine, Johns Hopkins Univ.
J. Haddad	Endocrine Section, Dept. of Medicine, Univ. of Pennsylvania, Phila., PA.
C. Frondoza	Oncology Center, Johns Hopkins University, Baltimore, MD

## LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

13.0

## PROFESSIONAL:

9.2

## OTHER:

3.8

## CHECK APPROPRIATE BOXES)

☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes studies on the regulation of mineral metabolism and the pathophysiology of osteopenia in aging. These findings summarize investigations on:

1. The loss with age of bone mineral from rat femurs, measured by single photon absorptiometry.
2. Bone status of the aging female rat.
3. Mineral homeostasis and skeletal histology in the aged female rat.
4. Characterization of the human osteosarcoma cell line (CRL-1427) as a model osteoblast-like human bone cell.
5. Regulation of bone resorption by a phenylalkylamine-sensitive calcium channel.
6. Biochemical mechanism of the age-associated decrease in vitamin D-sensitive intestinal calcium absorption.
7. Desensitization to PTH in Renal Cells from Aged Rats is Associated with a Decrease in PTH Receptor Binding Sites.
8. Desensitization to PTH in Renal Cells from Aged Rats Can Be Reversed by Parathyroidectomy of the Senescent Animal.
9. Preparation of cDNAs for Gs, Gi, Go and actin.
10. Pertussis Toxin Blocks the Action of  $\alpha_2$ -Adrenergic Hormones in Blunting the Response of Renal Cells to PTH.
11. PTH Regulation of Cytosolic  $\text{Ca}^{2+}$  in Proximal Tubules.
12. The PTH-Induced Increase in Cytosolic  $\text{Ca}^{2+}$  is Desensitized by PTH.
13. The PTH-Induced Increase in cAMP in OK Cells is Desensitized by PTH.
14. The Concentration of Ionized Ca in Serum is Unaltered in the Aged Male Rat.
15. Regulation of PTH-Independent Phosphate Uptake in Cultured Renal Cells (OK Cells) by Calcium.
16. PTH Enhances 25(OH)vit. $\text{D}_3$  1-Hydroxylase Activity in Renal Cells.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00052-07 L8C

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulatory Mechanisms in the Control of Cell Functions: Effects of Age.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Bertram Sacktor	Chief, Laboratory of Biological Chemistry	LBC GRC NIA
C. Filburn	Research Chemist	LBC GRC NIA
J. Kinsella	Research Physiologist	LBC GRC NIA
S. Guggino	Senior Staff Fellow (MBS)	LBC GRC NIA
R. Prasad	Visiting Fellow	LBC GRC NIA
H. Yamada	Visiting Fellow	LBC GRC NIA
K. Yonemura	Visiting Fellow	LBC GRC NIA
K. Otsu	Visiting Fellow (MBS)	LBC GRC NIA
J. Froehlich	Chief, Membrane Biology Section	LBC GRC NIA

## COOPERATING UNITS (if any)

W. Guggino Dept. of Physiol., Johns Hopkins Univ., School of Medicine

## LAB/BRANCH

Gerontology Research Center, Laboratory of Biological Chemistry

## SECTION

Regulatory Mechanisms Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

8.1

## PROFESSIONAL:

5.5

## OTHER:

2.6

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews
- ☒ (b) Human tissues
- ☐ (c) Neither

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This report describes studies on the biochemical and physiological mechanisms by which cell functions are regulated by hormones, agonists, and in pathophysiological states, including aging. The findings summarize investigations on:

1. Investigations of the  $\text{Na}^+\text{-H}^+$  Exchange Mechanism.
2. Thyroid hormone regulation of  $\text{Na}^+\text{-H}^+$  exchange activity.
3. Effect of L-Triiodothyronine ( $\text{T}_3$ ) on  $\text{Na}^+\text{-H}^+$  Exchange Activity in Cultured Kidney (OK) Cells.
4. Renal  $\text{Na}^+\text{-H}^+$  Exchange Activity in Aged Rats.
5. Effects of Ovariectomy and Estrogen Replacement on Renal Water and Electrolyte Metabolism in Rats.
6. Dopamine Increases Cytosolic Calcium in Renal Proximal Tubules.
7. Age-Associated Changes in Hormone-Induced Membrane Signal Transduction Systems in Renal Proximal Tubules.
8. Signal Transduction Mechanisms in Murine Splenic Lymphocytes.
9. Bradykinin Induces Changes in Cytosolic Calcium in Human Fibroblasts (IMR-90).
10. Mechanism of the Decrease in Renal Ammonia Excretion After an Acid Load in Aged Rats.
11. Modulation of the  $\text{Ca}^{2+}$ -activated  $\text{K}^+$  Channel in Medullary Thick Ascending Limb Cells.





<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE</b> <b>NOTICE OF INTRAMURAL RESEARCH PROJECT</b>		PROJECT NUMBER  Z01 AG 00048-13 LBC
PERIOD COVERED <b>October 1, 1986 to September 30, 1987</b>		
TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) <b>Ion Transport Mechanisms and Aging</b>		
PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation) <b>Jeffrey P. Froehlich</b> Medical Officer, Chief, Membrane Biol Sec <span style="float: right;">LBC GRC NIA</span> Other: <b>Phillip F. Heller</b> Chemist <span style="float: right;">LBC GRC NIA</span> <b>Kinya Otsu</b> Visiting Fellow (EOD 12/1/84) <span style="float: right;">LBC GRC NIA</span> <b>Sandra Guggino</b> Senior Staff Fellow <span style="float: right;">LBC GRC NIA</span> <b>Bertram Sacktor</b> Chief, Laboratory of Biological Chemistry <span style="float: right;">LBC GRC NIA</span> <b>James Kinsella</b> Research Physiologist <span style="float: right;">LBC GRC NIA</span> <div style="text-align: right;">cont'd</div>		
COOPERATING UNITS (if any)  Department of Physiology, University of Virginia School of Medicine Laboratory of Neurochemistry, NINCDS, NIH, Bethesda, MD.		
LAB/BRANCH Gerontology Research Center, Laboratory of Biological Chemistry		
SECTION Membrane Biology Section		
INSTITUTE AND LOCATION NIA, NIH, Baltimore, MD 21224		
TOTAL MAN-YEARS: <b>4.3</b>	PROFESSIONAL: <b>3.6</b>	OTHER: <b>0.7</b>
CHECK APPROPRIATE BOX(ES) <input type="checkbox"/> (a) Human subjects <input type="checkbox"/> (b) Human tissues <input checked="" type="checkbox"/> (c) Neither <input type="checkbox"/> (a1) Minors <input type="checkbox"/> (a2) Interviews		
SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)  Kinetic investigations of the enzymatic and transport reactions of the $\text{Ca}^{2+}$ pump in sarcoplasmic reticulum (SR) labelled with <u>fluorescein isothiocyanate</u> have uncovered new evidence for the existence of <u>protein subunit interactions</u> in the mechanism of <u>active <math>\text{Ca}^{2+}</math> translocation</u> . The results suggest that subunit conformational interactions are involved in recycling of the transport site following $\text{Ca}^{2+}$ transport. <u>Three distinct passive <math>\text{Ca}^{2+}</math> efflux components</u> have been resolved in passively-loaded SR membrane vesicles isolated from rat myocardium. The absence of an age difference in $\text{Ca}^{2+}$ efflux suggests that the age-related decline in active $\text{Ca}^{2+}$ transport is not due to an increased passive $\text{Ca}^{2+}$ leak. Determination of the $[\text{Na}^+]$ dependence of the <u><math>\text{Na}^+\text{-H}^+</math> exchanger</u> over an extended range of concentrations has revealed a new class of <u>high affinity <math>\text{Na}^+</math> binding sites</u> that participate in $\text{Na}^+$ translocation. The kinetic features of the $\text{Na}^+\text{-H}^+$ exchanger are consistent with a <u>tetrameric subunit model</u> in which the sites become sequentially available to transport $\text{Na}^+$ after the initial turnover. Two $\text{Na}^+$ -i-independent <u><math>\text{Ca}^{2+}</math> translocation pathways</u> have been identified in <u>cardiac sarcolemmal vesicles</u> that exhibit differential sensitivity to <u>inorganic <math>\text{Ca}^{2+}</math> channel blockers</u> . The pharmacologic and kinetic behavior associated with these pathways suggests that they might be involved in mediation of the <u>transient and slow inward <math>\text{Ca}^{2+}</math> currents</u> in cardiac muscle.		



ANNUAL REPORT OF THE LABORATORY OF CARDIOVASCULAR SCIENCE  
NATIONAL INSTITUTE ON AGING

The overall goals of the Laboratory of Cardiovascular Science are (1) to identify age-related changes that occur within the cardiovascular system and to determine the mechanisms for these changes; (2) to study myocardial structure and function, and response to pharmacological therapeutics in mechanical overload, altered thyroid state, and physical conditioning models, and to determine how age interacts with these altered cardiac states to determine the level of myocardial function; and (3) to study basic mechanisms in excitation-contraction coupling and of energy-yielding oxidative pathways in cardiac muscle. In meeting these objectives, studies are performed in human volunteers, intact animals, isolated heart and vascular tissues, isolated cardiac cells, and subcellular organelles.

Cardiac Function Section

Research of this Section is in both human and animal models and in tissues and cells from animal models. Our studies in man utilize state of the art technology to study the impact of age on cardiovascular function at rest and during exercise stress, when adrenergic modulation of the circulatory system is maximum. Subjects for this research are drawn from participants in the Baltimore Longitudinal Study of Aging (BLSA). Our purpose is not only to describe age-related changes per se but to determine mechanisms that underlie these changes. To meet this purpose, pharmacologic perturbations are employed in these studies, particularly those that pertain to the cardiovascular autonomic modulation. In animal models (rat and beagle dog), a more specific mechanistic approach is taken to investigate the direct effects of aging, cardiovascular overload state, physical conditioning, and pharmacologic perturbations on myocardial and vascular tissues. In addition, mechanisms of excitation-contraction coupling are explored in these isolated tissues. More specific yet are our studies on single cardiac<sub>2+</sub> myocytes, particularly those that deal with the regulation of cytosolic  $Ca^{2+}$ , and  $Ca^{2+}$ -induced  $Ca^{2+}$  release as a mechanism to couple excitation-contraction, and as manifest in spontaneous diastolic  $Ca^{2+}$  oscillations, as a potent modulator of both systolic and diastolic function, particularly in disease states when control of cell  $Ca^{2+}$  regulation may be deficient. Finally, studies in cardiac subcellular organelles, e.g. myofibrils, sarcoplasmic reticulum, probe the effects of aging, chronic physical conditioning, and cardiac overload states. This approach, in some instances, results in unique "vertical data" from man to organelle, e.g. those studies of autonomic modulation of cardiac function and its modification due to aging.

Energy Metabolism and Bioenergetics Section

The objective of this Section is to identify and characterize mechanisms whereby oxidative metabolism is enhanced in response to the energy-demands created by the increased performance of work; further, it is our endeavor to describe rearrangements in these control mechanisms which may occur during aging. Many of our studies involve cardiac muscle preparations, and the energy-demands reflect mainly those of contraction. In this case, the  $Ca^{2+}$  ion which forms the link between excitation and contraction also activates mitochondrial substrate oxida-



tion and therefore energy-provision, a relationship which we have recognized in the phrase "excitation-contraction-metabolism coupling." Studies are carried out at the level of isolated cardiac myocytes, isolated mitochondria and purified enzymes. As many of the animal model studies of the Cardiac Function Section are concerned with the role of  $\text{Ca}^{2+}$  ions in stimulating contraction, our work is complementary, and there is scope for the closest interaction between the Sections. Other experimental paradigms being pursued in this Section include the stimulation by  $\text{Ca}^{2+}$ -mobilizing hormones of the energy-requiring gluconeogenic pathway in hepatocytes, and the role of  $\text{Ca}^{2+}$  ions in activating the synthesis of the neurotransmitter acetylcholine, as well as in the mediation of its release. The latter studies are carried out with preparations of presynaptic vesicles and are currently the focus of the aging studies of the Section.

During FY 1987 our studies have continued to range in scope from man to mechanistic studies of myocardial contraction and cell energetics.

### Studies in Man

#### Factors Determining Maximal exercise performance in man

Maximal oxygen consumption ( $\text{VO}_{2\text{max}}$ ) during treadmill exercise has been performed in nearly 700 BLSA volunteers over the past 7 years. In a carefully selected nonobese group of 83 men and 101 women without exercise-induced ischemia,  $\text{VO}_{2\text{max}}$  expressed in  $\text{ml/kg}$  body weight/min declined sharply with age (men:  $\text{VO}_{2\text{max}} = 54.9 - 0.39 \text{ age}$ ,  $r^2 = .60$ ; women:  $\text{VO}_{2\text{max}} = 41.0 - 0.25 \text{ age}$ ,  $r^2 = .50$ , both  $p < .0001$ ). After normalization for 24 hour urinary creatinine excretion, an index of total body muscle mass, the age decline in  $\text{VO}_{2\text{max}}$  was markedly attenuated in both sexes (men:  $r^2 = .14$ , women:  $r^2 = .08$ ). To determine the role of physical activity in preserving functional capacity with advancing age, we have measured  $\text{VO}_{2\text{max}}$ , body composition, blood lipid, glucose tolerance, and cardiac volumes at rest, during maximal treadmill exercise in 19 highly trained men 60-76 years old. Whereas  $\text{VO}_{2\text{max}}$  ( $51 \pm 1$  versus  $30 \pm 2$  and HDL cholesterol ( $59 \pm 3$  versus  $49 \pm 3$ ) were significantly higher than in age matched nonathletic controls, plasma LDL, fasting and 2 hr postcardial glucose were lower. Preliminary data during upright bicycle exercise suggest that both L ventricular end diastolic volume and stroke volume are greater and heart rate lower at any submaximal load than in control subjects.

The metabolic effects of relatively prolonged submaximal treadmill exercise is being studied in normal BLSA men. Preliminary results suggest a significant age-related augmentation of plasma catecholamines after 45-60 min of exercise, similar to that previously found in BLSA men during short-term maximal treadmill testing. The response to maximal upright bicycle exercise in over 30 BLSA subjects with exercise-induced myocardial ischemia detected by ECG or thallium scan is being compared with that of age-related nonischemic BLSA controls. Gender differences in the hemodynamic response to bicycle exercise are also being explored.

#### Exercise-Induced Cardiac Arrhythmias

We compared the prevalence and complexity of exercise-induced arrhythmias in BLSA subjects on chronic diuretic monotherapy for hypertension with that in normotensive control group. Although the prevalence of exercise induced arrhythmias was higher in the diuretic treated group (D) than in controls (C) 57% vs





38%,  $p < .05$ , this difference was due entirely to the higher prevalence of simple ventricular ectopic beats (VEB): 44% versus 26%,  $p < .05$ . No difference between the groups was found in the prevalence of frequent or complex ectopic beats.

Between 1974 and 1984, 80 BLSA subjects (6.9% of those tested), developed frequent ( $> 10\%$  of beats in any minute) ventricular ectopic beats (VEB) or runs of 3 or more VEB on at least one maximal treadmill exercise test. Those developing frequent or repetitive VEB were older than the remaining subjects  $63.8 \pm 12.5$  vs  $50.0 \pm 16.1$  yr,  $p < .0001$ . Within the former group, an ischemic ST segment response to exercise was observed in only 11%. Over a mean follow-up period of 4.6 years without anti-arrhythmic drug therapy, only one cardiac death and one non-fatal myocardial infarction have occurred.

To investigate the mechanisms for exercise-induced complex ventricular arrhythmias in apparently healthy subjects, we compared repolarization time, i.e. QT intervals, in 20 BLSA subjects with exercise induced nonsustained ventricular tachycardia (VT) with those of 20 normal BLSA individuals matched for age and sex, who were free of exercise-induced arrhythmias. Although no difference in heart rate was present at rest or at maximal effort between groups, those with exercise-induced VT had longer QT intervals than the controls ( $278 \pm 9$  vs  $259 \pm 6$  msec,  $p < .08$ ). Whereas 12 of 20 VT subjects failed to shorten their QT interval by 25% only 5 of 20 controls demonstrated this finding,  $p < .05$ .

#### Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm.

To assess the ability of maintenance digoxin therapy to improve exercise tolerance in patients with stable CHF, systolic dysfunction and sinus rhythm, we performed maximal treadmill exercise tests in 12 such individuals while monitoring respiratory gas exchange. No difference in exercise duration, maximal oxygen consumption ( $VO_{2max}$ ), maximal heart rate, or ventilation was found after 4 weeks of digoxin versus 4 weeks of placebo in a randomized crossover study. During maximal upright bicycle exercise, however, digoxin increased ejection fraction from .26 to .31 despite identical exercise tolerance.

Our group has initiated the development of a questionnaire in conjunction with experts in cardiology at different universities to sample representative groups of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. Among 2704 questionnaire respondents diuretics alone were considered the best initial therapy for CHF in 50%, digitalis alone by 8% and the combination in 33%. Two thirds of the sample felt that digitalis improved exercise tolerance. Thus, despite growing evidence that digitalis glycosides can be successfully withdrawn from patients with chronic stable CHF, widespread belief persists that these drugs are effective in most CHF patients. Analysis of outpatient laboratory utilization revealed that general/family practitioners saw their CHF outpatients more frequently but were less likely to employ echocardiography or radionuclide ventriculography than were cardiologists, with internists falling in between. Overall annual cost of following a stable CHF outpatient varied from \$621 for





general practitioners to \$762 for cardiologists.

#### Detection and Prognosis of Silent Myocardial Ischemia

To ascertain whether the addition of exercise thallium scintigraphy (TS) would enhance the prediction of future cardiac events in clinically healthy subjects, we performed both ECG and TS with maximal treadmill exercise in 409 volunteers (aged 40-92 yr) from the BLSA who were free of cardiac disease by history, physical examination, and resting ECG. Over a mean followup interval of 4.6 yr (range 1.5-8.5), 42 coronary events were recorded. The predictive value for a coronary event in the 23 subjects (5.6% of sample) with both ischemic ECG and abnormal TS was 48%. By logistic regression analysis, the combination of ischemic ECG and abnormal TS predicted a 6.3 fold relative risk of a subsequent coronary event, independent of conventional risk factors (age, sex, smoking status, hypertension, total cholesterol). Thus, the combination of ischemic ECG and abnormal TS in totally asymptomatic subjects is a potent predictor of future coronary events.

Among 696 apparently healthy subjects from the BLSA who have undergone serial maximal exercise treadmill testing since 1977, the risk of subsequent cardiac events was compared in those whose initial test was positive (Group I) versus those converting from a negative to a positive test (Group II) over a 5.7 yr mean followup.

	<u>Group I</u>	<u>Group II</u>
n	70	80
age	64	62
men (%)	54*	86
events	11	9
events/yr (%)	2.6	2.1

\*p<.01 by Chi square analysis

Thus in asymptomatic subjects, serial conversion from a negative to a positive exercise ECG is of no greater predictive value for a future coronary event than an initially positive response.

#### Mechanistic Studies of Myocardial Contraction and Cell Energetics in Animal Tissues

##### Excitation-Contraction in Isolated Cardiac Cells

We have dissociated cardiac cells from adult rats, rabbits and guinea pigs. These preparations are being used to study the contractile, electrophysiological, and biochemical characteristics in a variety of different conditions. We have developed a system for simultaneous measurement, in single cardiac myocytes, of changes in cytosolic free calcium, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe indo-1 to monitor cytosolic free calcium transient. Indo-1 fluorescence is excited by epi-illumination with 10 microsecond flashes of 350 + 10 nm light at repetition rates of up to 200 Hz. Indo emission is collected by paired photomultipliers to measure simultaneously spectral windows of 411 + 20 nm and 481 + 25 nm optimizing the trade-off between collected light intensity and cytosolic free calcium sensitivity. The fluorescence emission from each flash is collected by a pair of fast integrator sample-and-hold circuits of custom



design under the control of a VAX 11/730 computer which computes the ratio of indo emission at the two wavelengths as a measure of cytosolic free calcium with a time precision of better than 20 microseconds. Cells length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector (or a photodiode array when millisecond time resolution is required). The membrane potential may be monitored simultaneously with patch electrodes. Our initial results have shown the widely divergent, calcium-dependent systolic and diastolic properties of intact rat, guinea pig and rabbit cardiac muscle are retained with a high degree of fidelity in the majority of viable single myocytes isolated from the myocardium of these species, and that these myocytes are thus a valid model for studies of calcium-dependent excitation-contraction mechanisms in the heart. Thus, the availability of single myocytes and an apparatus whereby we can simultaneously measure membrane currents, cytosolic calcium and function will permit mechanistic studies of aspects of excitation-contraction coupling that have heretofore not been amenable to direct study. We have already begun some initial experiments of this sort.

#### Beta-Adrenergic Modulation of Myocyte $Ca^{2+}$ , Membrane Currents, and Contraction

Beta-adrenergic agonists increase the myocardial contraction strength and enhance relaxation. Calcium is a critical agent in the activation and relaxation of contraction in the heart. When calcium binds to the myofilaments, contraction is initiated; when calcium comes off the myofilaments, relaxation occurs. Two possible determinants of relaxation are: (1) the sensitivity of the myofilaments for calcium, and (2) calcium sequestration e.g. by the sarcoplasmic reticulum (SR). The contractile enhancement by beta-adrenergic agonists is due to an increase in the calcium released into the myoplasmic space. Whether beta-adrenergic stimulation specifically abbreviates the cytosolic calcium transient, measured via the calcium indicator aequorin in intact muscle, is controversial. We examined the effect of isoproterenol,  $5 \times 10^{-6}$  M, on cytosolic calcium transient (measured via indo 1 fluorescence 410 nm/490 nm) membrane potential and cell shortening during the twitch (video edge detector) in single rat and guinea pig cardiac myocytes. In guinea pig cells isoproterenol (0.1  $\mu$ M) increased the peak calcium current 3-fold. The 4-fold larger estimated calcium entry (integrated area of calcium current) contributes to the estimated augmentation of contraction. The steady state myoplasmic calcium transient rose with 2.7 fold larger rate to a 2.7 fold higher peak and was reached after 65 instead of 300 ms after the start of depolarization. Isoproterenol accelerated the decay of the calcium transient 4.4 fold. Thus, the beta-adrenergic agonist, isoproterenol, not only potentiates the twitch but also leads to more rapid and complete relaxation of the myoplasmic calcium transient under the present conditions. This may account for the accelerated relaxation of contraction.

#### Effect of Alpha-Adrenergic Stimulation on Isolated Ventricular Myocytes

Alpha-adrenergic stimulation is known to lead to the formation of at least two second messengers, inositol trisphosphate ( $IP_3$ ) which is thought to release  $Ca^{2+}$  from the sarcoplasmic reticulum (SR) and 1,2 diacylglycerol (DAG) which activates a  $Ca^{2+}$ -dependent protein kinase, i.e. protein kinase C (PKC). Previous work done in our laboratory showed that both DAG and the tumor promoting agent phorbol ester increase membrane activation of PKC and have a negative inotropic effect in adult cardiac myocytes. We hypothesized that



because of its  $\text{Ca}^{2+}$ -dependence that during high cell  $\text{Ca}^{2+}$  loading PKC activation would be more marked than under normal cell  $\text{Ca}^{2+}$  loading and possibly determine a negative inotropic effect of alpha-adrenergic stimulation rather than the better known positive response which could be related to the action of  $\text{IP}_3$  to release  $\text{Ca}^{2+}$  from the SR.

Isolated rat ventricular myocytes, pretreated with propranolol were used to investigate the effect of alpha-adrenergic stimulation with phenylephrine on the frequency of spontaneous contractile waves (CW), which represent the mechanical expression of spontaneous  $\text{Ca}^{2+}$  release from the SR, and on twitch amplitude (TA). CW were measured in the unstimulated state and TA was determined during field stimulation. a. In the absence of stimulation, in 5 mM  $\text{Ca}_0$  treatment with phenylephrine led to a significant reduction in CW frequency and this was reversible upon removal of the drug. b. In cells stimulated to contract at a rate of 0.2 Hz, in 5 mM  $\text{Ca}_0$  CW appeared in some of the diastolic intervals. Treatment with phenylephrine caused abolition of diastolic CW and a significant diminution in TA. This negative effect of phenylephrine was in contrast to a positive inotropic action observed in parallel studies in 1 mM  $\text{Ca}_0$ . These findings are consistent with the view that the effect of alpha-adrenergic stimulation of cardiac cells can vary in relation to intracellular  $[\text{Ca}^{2+}]_i$ .

#### Role of Calcium in the Regulation of Energy Metabolism

This project is designed to assess the physiological importance of calcium ions in the regulation of energy metabolism. We have exposed isolated rat cardiac myocytes to a variety of agents and conditions expected to alter cytosolic free calcium ion concentration and have measured the rate of  $\text{O}_2$ -uptake by the cell suspensions, as well as the cellular content of NADH. Further, we have estimated cytosolic calcium concentration using fluorescent chelating agents, in parallel experiments performed under identical conditions. In each case, there was a good correlation between the magnitude of the increase in calcium concentration and the degree of stimulation of  $\text{O}_2$ -uptake. Attempts were made to assess the quantitative significance of direct activation of respiration by calcium ions at the level of mitochondrial dehydrogenases versus an indirect mechanism involving increased ADP generation. Ruthenium red, which blocks the former process but not the latter, gave a small decrease in rates of  $\text{O}_2$ -uptake. However, activation of oxidative phosphorylation by ADP was a predominant mechanism, based on the lowered mitochondrial content of NADH which was observed to occur in response to calcium mobilization.

#### Cellular $\text{Ca}^{2+}$ Ion Homeostasis and the Impact of Aging

This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of cytosolic free  $\text{Ca}^{2+}$  concentrations ( $[\text{Ca}^{2+}]_i$ ), and allow perturbations in  $[\text{Ca}^{2+}]_i$  in response to hormones and neurotransmitters. Further, it addresses derangements in these control mechanisms which may occur in old-age. This year, we have asked the following questions. (1) What is the mechanism whereby the hormone glucagon leads to an increase in  $[\text{Ca}^{2+}]_i$  in hepatocytes? The efficacy of cyclic-AMP analogues in raising  $[\text{Ca}^{2+}]_i$  and the similar dose-response to glucagon of changes in  $[\text{Ca}^{2+}]_i$  and changes in the activity of pyruvate kinase, which is phosphorylated by protein kinase A, have suggested to us that a mechanism involving solely protein kinase A is sufficient, though other mechanisms cannot be excluded. (2) What membrane carrier proteins are involved in mediating the entry of  $\text{Ca}^{2+}$  into myocytes when







they are treated with veratridine? This  $Ca^{2+}$  compound potentiates  $Na^+$ -channel activity and leads to a large increase in  $[Ca^{2+}]_i$ , an effect which we have found to be a useful tool in simulating a high work-load for our metabolic studies in myocytes. We have sought to distinguish between an involvement of  $Ca^{2+}$  channels and  $Na^+/Ca^{2+}$  exchange by using the inhibitors verapamil, nitrendipine,  $Cd^{2+}$  and dichlorobenzamil, and have obtained answers indicating that the contribution of these two processes to total flux varies with the extracellular  $Na^+$ ,  $H^+$  and  $Ca^{2+}$  concentrations and the degree of depolarization. (3) Are there distinct  $\alpha$ - and  $\beta$ -adrenergic effects on the depolarization-induced entry of  $Ca^{2+}$  into cardiac myocytes? We have studied cells loaded with Quin-2 and have identified a novel interaction, such that  $Ca^{2+}$  flux is activated more by  $\beta$ -agonists alone than by  $\alpha$ - and  $\beta$ -agonists together. (4) Are there correlates at the level of protein phosphorylation of the previously described decreased responsiveness of  $Ca^{2+}$  transport to catecholamines in the aging heart? We have identified a decreased phosphorylation of troponin in myocytes from senescent rats and are currently focussing on phospholamban.

### Structure and Function of Single Cardiac Myocytes Over a Broad Age Range

There has been considerable prior work from this laboratory as well as others documenting that the time course of cardiac contraction in bulk muscle is prolonged with aging. Common measures of inotropy such as the maximal rate or amplitude of tension development appear unchanged with age. However, alterations in the cardiovascular response to stress occur with aging and have been attributed, in part, to a diminished effect of autonomic modulation of cardiovascular function. Whether these measurements represent fundamental characteristics of aging cells or are a reflection of an altered cellular composition of bulk muscle is unclear. Furthermore, what aging-associated alterations, if any, characterize the contractile properties of the fundamental contractile unit, the sarcomere, are unknown. We therefore measured the maximal velocity, amplitude, and time course of unloaded contractions of single isolated cardiac myocytes obtained from rats 2, 8, and 24 months old. We also combined these measurements with data on cell and sarcomere lengths which we have previously determined in similar cells. We find that the prolongation of the time course of contraction that occurs with aging is a fundamental property of the myocyte and must reflect changes in the basic processes governing excitation-contraction coupling. The maximal rate or extent of shortening of individual sarcomeres is unaltered with aging, and the series addition of sarcomeres (which we have previously shown to characterize the aging heart) appears to be an adaptation that may permit the aging heart to meet the challenge of the increased load against which it must function. A decreased contractile response to norepinephrine with adult aging can also be demonstrated directly in cardiac myocytes. This deficit may be specific to catecholamines since the response to a non-adrenergic calcium channel agonist, BayK, is not age-related.

### Cardiac Muscle Properties in Senescent Rats is not Related to Serum Urea Levels

One of the most striking changes in the cardiovascular system which accompanies advancing age is the prolongation of the duration of systole. This age-associated prolongation occurs in man, lower mammals, and in rodents, and apparently represents an age related change in cardiac muscle across species. However, advancing age in rodents is also often accompanied by a progressive



decline in renal function, making it difficult to partition cardiovascular changes into truly age-related versus renal related declines. In order to determine whether myocardial function in senescent (24 mo) male Wistar rats varies with SUN, we measured function of isolated cardiac muscle from animals with higher and lower SUN. Muscles were bathed in normal Ringer's bicarbonate solution ( $[Ca] = 1.0 \text{ mM}$ ) and stimulated to contract 24 min at  $30^\circ\text{C}$  at  $L_{max}$ . The mean  $\pm$  SEM, SUN, resting tension (RT), developed twitch tension (TT), maximum rate of tension rise ( $dt/dt_{max}$ ) and contraction duration (CD) in the two groups were:

SUN	p<.000	N	RT (g/mm <sup>2</sup> )	TT (g/mm <sup>2</sup> )	dt/dt (g/mm <sup>2</sup> /max sec)	CD (msec)
60.83	±2.31	6	1.46±.28	3.19±.46	35.45±4.88	283±7
26.14	±1.44	7	1.45±.42	3.23±.64	36.74±7.96	290±8

Thus, these contractile properties of isolated cardiac muscle do not depend on SUN. Additionally, the maximum contractile response to isoproterenol ( $10^{-5} \text{ M}$ ) did not vary with SUN ( $dt/dt = 34 \pm 6$  vs  $21 \pm 9\%$  control in the high and low SUN group respectively. We conclude that contractile function in cardiac muscle from senescent rats is not affected by the levels of SUN encountered in these rats.

#### Pathophysiologic Effects of Spontaneous $Ca^{2+}$ Release in the Heart

All mammalian cardiac preparations, given sufficient  $Ca^{2+}$  loading, exhibit spontaneous release of  $Ca^{2+}$  from the sarcoplasmic reticulum (SR). Videomicroscopy in muscle and myocytes has shown that the myofilament motion due to this type of  $Ca^{2+}$  release is (1) spatially non-uniform and (2) propagates at approximately 100  $\mu\text{m/sec}$  as a contractile wave, indicating that the spontaneous  $Ca^{2+}$  release occurs locally, and, in diffusing down its concentration gradient, causes a regenerative  $Ca^{2+}$  induced  $Ca^{2+}$  release from the SR. The localized  $[Ca^{2+}]$  achieved as result of spontaneous SR release has been estimated to range from a few  $\mu\text{m}$  to 40  $\mu\text{m}$ . Myofilaments in areas of high  $Ca^{2+}$  shorten and stretch neighboring myofilaments where  $[Ca^{2+}]$  is lower. Since, in bulk cardiac tissue this occurs asynchronously among cells, quiescent cells are stretched and therefore sarcomere loading in these cells is affected. The net result of these events is  $Ca^{2+}$ -dependent diastolic tonus. The diastolic oscillatory  $Ca^{2+}$  modulation of sarcolemmal ion conductances within areas of high  $Ca^{2+}$  results in sarcolemmal depolarization, which, if sufficient in magnitude, triggers a spontaneous action potential and leads to arrhythmias. Finally, the resultant inhomogeneity in the extent of SR  $Ca^{2+}$  loading and phases of SR  $Ca^{2+}$  recycling that occur in the presence of spontaneous SR  $Ca^{2+}$  release cause a reduction in the net extent and synchrony of systolic  $Ca^{2+}$  release from the SR by a subsequent action potential. This impairs systolic function. Enhanced diastolic tone, the occurrence of arrhythmias, and compromised systolic function are cardinal signs of many myocardial disease states. The conceptualization of spontaneous SR  $Ca^{2+}$  release as interpreted and discussed in the context of the present findings in cardiac myocytes, though speculative in some regard, provides a logical framework in which no structure testable hypotheses about its potential role in the pathophysiology of some forms of heart disease.

#### Myocardial Calcium Oscillations During Reperfusion and Reoxygenation

The full extent of myocardial contractile recovery following ischemia is delayed beyond the immediate reperfusion (R). This may be associated with delayed



metabolic recovery and/or  $\text{Ca}^{2+}$  overload. This can be quantified in the beating heart by the scattered laser intensity fluctuations (SLIF) which senses  $\text{Ca}$  oscillations ( $\text{CaOs}$ ) it produces. We measured ATP, and pH by  $^{31}\text{P}$  NMR and SLIF, and developed pressure in isovolumic rat hearts. During the first 5 min of R there is rapid metabolic but a more gradual developed pressure and SLIF recovery. Then both gradually recover developed pressure abruptly and SLIF increases fourfold over the next 40 min mean no change in metabolic parameters. These findings suggest that delayed contractile recovery during R is attributable in part to an adverse effect of increased  $\text{CaOs}$  induced by  $\text{Ca}^{2+}$  overload during R. In additional hearts, for the first 10 min of R, perfusate  $\text{Ca}$  was 1.5 mM (Group 1, n = 4) or 0.08 mM (Group 2, n = 4). During R the early peak in SLIF was not present in Group 2. Recovery of DP was higher and cell  $\text{Ca}$  lower in Group 2 vs Group 1 at 20 min R. Thus,  $\text{CaOsc}$  during early R are modified by perfusate  $\text{Ca}$ , noninvasively index the extent of  $\text{Ca}$  loading, and predict functional recovery.

Other hearts were pretreated with Amiloride  $10^{-4}$ , a known Na-Ca blocker during hypoxia and reoxygenation ( $\text{ReO}_2$ ). During  $\text{ReO}_2$ , DP, EDP and PCr (all % baseline), and pH<sub>i</sub> recovery were improved in the Amiloride treated hearts. Cell gain during  $\text{ReO}_2$  was reduced 50% by Amiloride. These results suggest that cell  $\text{Ca}$  loading during reoxygenation is Na dependent and may be mediated in part by Na/Ca exchange.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00029-10 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Efficacy of Digitalis in Congestive Heart Failure and in Normal Subjects

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Francis Scott Key Medical Center, Baltimore, MD (S. H. Gottlieb), Peter Bent Brigham Hosp., Boston, MA (T. Smith), University of Arizona, Tucson, AZ (F. Marcus), Massachusetts General Hospital, Boston, MA (R. Johnson), Duke University, Durham, NC (H. Strauss and M. Hlarky)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NTA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.2

## PROFESSIONAL:

0.1

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard, unabbreviated type. Do not exceed the space provided.)

We have previously shown in a double-blind crossover study that digitalis could be discontinued for three months without adverse clinical effect and only minor changes in cardiac size and function in 30 subjects with stable congestive heart failure (CHF) and sinus rhythm.

To assess the ability of maintenance digoxin therapy to improve exercise tolerance in patients with stable CHF, systolic dysfunction and sinus rhythm, we performed maximal treadmill exercise tests in 12 such individuals while monitoring respiratory gas exchange. No difference in exercise duration, maximal oxygen consumption ( $\text{VO}_2\text{max}$ ), maximal heart rate, or ventilation was found after 4 weeks of digoxin versus 4 weeks of placebo in a randomized crossover study. During maximal upright bicycle exercise, however, digoxin increased ejection fraction from .26 to .31 despite identical exercise tolerance.

Our group has initiated the development of a questionnaire in conjunction with experts in cardiology at different universities to sample representative groups of academic and practicing physicians in their current use and understanding of the effectiveness and toxicity of digitalis glycosides. Among 2704 questionnaire respondents diuretics alone were considered the best initial therapy for CHF in 50%, digitalis alone by 8% and the combination in 33%. Two thirds of the sample felt that digitalis improved exercise tolerance. Thus, despite growing evidence that digitalis glycosides can be successfully withdrawn from patients with chronic stable CHF, widespread belief persists that these drugs are effective in most CHF patients. Analysis of outpatient laboratory utilization revealed that general/family practitioners saw their CHF outpatients more frequently but were less likely to employ echocardiography or radionuclide ventriculography than were cardiologists, with internists falling in between. Overall annual cost of following a stable CHF outpatient varied from \$621 for general practitioners to \$762 for cardiologists.





DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00035-08 LCS

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Fluctuations in the Intensity of Light Scattered thru Diastolic Cardiac Muscle

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA  
Others: M. D. Stern IPA LCS, NIA  
R. Weiss Medical Staff Fellow LCS, NIA

COOPERATING UNITS (if any) Cardiology Division, Dept. Medicine, Johns Hopkins Hosp., Baltimore, MD (G. Gerstenblith, D. Renlund and E. Marban), Dept. Physiology, Univ. of Maryland, Baltimore, MD (W. G. Wier), Albany Med. Ctr., Albany, NY (A. A. Korr), Dept. Pharmacology, Southwestern Medical School, Dallas, TX (J. Sutko)

LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

SECTION

Cardiac Function Section

INSTITUTE AND LOCATION

NTA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

2.8

2.7

1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects

☐ (b) Human tissues

☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have discovered that scattered light intensity fluctuations (SLIF) are present in isolated rat ventricular muscle even under conditions formerly considered to be quiescent. Subsequent experiments indicated that SLIF are highly dependent on calcium loading of the cell and could be reversibly terminated (1) by maintaining constant calcium concentration in the myofilament space in skinned fibers or (2) in intact fibers by caffeine. These results were interpreted to indicate that cellular myoplasmic calcium concentration oscillates in diastole, producing motion of the myofilaments, which modulates the laser beam and results in SLIF. This myofilament motion which is asynchronous within a cell, and among cells, results in a small degree of diastolic force or "tone" in the muscle. Additional experiments have demonstrated SLIF in atrial, ventricular, and conduction tissues in a range of mammalian species including man and indicate the universality of this phenomenon in excitable cardiac tissues. We have directly demonstrated these calcium oscillations utilizing intracellular injects of the chemiluminescent protein, aequorin and modeled the effect of heterogeneous calcium oscillation on tonic force. We have also demonstrated the presence of SLIF in the intact perfused heart and have shown that it covaries with calcium-dependent tone. In our most recent studies we have determine the specific characteristics of myofilament motion that cause SLIF. We have also shown that ischemia suppresses synchronous calcium release and reperfusion exacerbated it.

Combined into Z01 AG 00243-01 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00038-06 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Evaluation of Peripheral Blood Flow in Normal Man by Plethysmography

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	E. S. Beard	Chemist	LCS, NIA

## COOPERATING UNITS (if any)

Department of Anesthesia and Critical Care, Johns Hopkins Hospital (G. Bause)

## LAB/BRANCH

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## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

60	30	30
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## CHECK APPROPRIATE BOX(ES)

- |  |  |                                      |
|--|--|--------------------------------------|
| <input checked="" type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors                   |  |                                      |
| <input type="checkbox"/> (a2) Interviews               |  |                                      |

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Although the incidence of degenerative changes in the blood vessels is well known to increase with advancing age, quantitative data on the changes in peripheral blood flow due to the aging process per se are lacking. Venous occlusion plethysmography has been shown to be the most accurate and reproducible method to measure peripheral arterial flow. We have used this method to evaluate peripheral blood flow in healthy subjects aged 20-83 years from the Baltimore Longitudinal Study of Aging (BLSA) both at rest and in response to post-occlusion hyperemia, which results in near-maximal flow. Neither resting nor post-occlusion hyperemic blood flow were related to age in these 146 BLSA men and women who underwent occlusions of 1, 2, and 3 minutes both at 26°C and 35°C. These results suggest that peripheral arterial flow is not limited by age per se in man.

In a second protocol, the response of peripheral blood flow to intravenous infusion of isoproterenol and sodium nitroprusside was determined by plethysmography in 25 healthy volunteers ages 25-84 years. The results of this study are pending.

Discontinued.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00226-05 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Excitation-Contraction in Isolated Cardiac Cells

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. C. Capogrossi	Senior Staff Fellow	LCS, NIA
Others:	H. A. Spurgeon	Physiologist	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	M. D. Stern	IPA	LCS, NIA
	A. Talo	Visiting Professor	LCS, NIA
	D. J. Pello	Biologist	LCS, NIA

## COOPERATING UNITS (if any)

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## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2

## PROFESSIONAL:

1.6

## OTHER:

0.4

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unindented type. Do not exceed the space provided.)

We have dissociated cardiac cells from adult rats, rabbits and guinea pigs. These preparations are being used to study the contractile, electrophysiological, and biochemical characteristics in a variety of different conditions. We have developed a system for simultaneous measurement, in single cardiac myocytes, of changes in cytosolic free calcium, cell length and membrane current/voltage, with high time resolution. The system uses the fluorescent probe indo-1 to monitor cytosolic free calcium transient. Indo-1 fluorescence is excited by epi-illumination with 10 microsecond flashes of  $350 \pm 10$  nm light at repetition rates of up to 200 Hz. Indo emission is collected by paired photomultipliers to measure simultaneously spectral windows of  $411 \pm 20$  nm and  $481 \pm 25$  nm optimizing the trade-off between collected light intensity and cytosolic free calcium sensitivity. The fluorescence emission from each flash is collected by a pair of fast integrator sample-and-hold circuits of custom design under the control of a VAX 11/730 computer which computes the ratio of indo emission at the two wavelengths as a measure of cytosolic free calcium with a time precision of better than 20 microseconds. Cells length is measured from the bright-field image of the cell by an optical edge tracking method using a video edge detector (or a photodiode array when millisecond time resolution is required). The membrane potential may be monitored simultaneously with patch electrodes. Our initial results have shown the widely divergent, calcium-dependent systolic and diastolic properties of intact rat, guinea pig and rabbit cardiac muscle are retained with a high degree of fidelity in the majority of viable single myocytes isolated from the myocardium of these species, and that these myocytes are thus a valid model for studies of calcium-dependent excitation-contraction mechanisms in the heart. Thus, the availability of single myocytes and an apparatus whereby we can simultaneously measure membrane currents, cytosolic calcium and function will permit mechanistic studies of aspects of excitation-contraction coupling that have heretofore not been amenable to direct study. We have already begun some initial experiments of this sort.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00228-04 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Exercise-Induced Cardiac Arrhythmias

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	M. McIvor	Medical Staff Fellow (OOD 6/25/87)	LCS, NIA

## COOPERATING UNITS (# any)

Yale University School of Medicine (G. Bause)

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Cardiac Function Section

## INSTITUTE AND LOCATION

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## TOTAL MAN-YEARS:

1.8

## PROFESSIONAL:

1.7

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We compared the prevalence and complexity of exercise-induced arrhythmias in BLSA subjects on chronic diuretic monotherapy for hypertension with that in normotensive control group. Although the prevalence of exercise induced arrhythmias was higher in the diuretic treated group (D) than in controls (C) 57% vs 38%,  $p < .05$ , this difference was due entirely to the higher prevalence of simple ventricular ectopic beats (VEB): 44% versus 26%,  $p < .05$ . No difference between the groups was found in the prevalence of frequent or complex ectopic beats.

Between 1974 and 1984, 80 BLSA subjects (6.9% of those tested), developed frequent ( $> 10\%$  of beats in any minute) ventricular ectopic beats (VEB) or runs of 3 or more VEB on at least one maximal treadmill exercise test. Those developing frequent or repetitive VEB were older than the remaining subjects  $63.8 \pm 12.5$  vs  $50.0 \pm 16.1$  yr,  $p < .0001$ . Within the former group, an ischemic ST segment response to exercise was observed in only 11%. Over a mean follow-up period of 4.6 years without anti-arrhythmic drug therapy, only one cardiac death and one non-fatal myocardial infarction have occurred. To investigate the mechanisms for exercise-induced complex ventricular arrhythmias in apparently healthy subjects, we compared repolarization time, i.e. QT intervals, in 20 BLSA subjects with exercise induced nonsustained ventricular tachycardia (VT) with those of 20 normal BLSA individuals matched for age and sex, who were free of exercise-induced arrhythmias. Although no difference in heart rate was present at rest or at maximal effort between groups, those with exercise-induced VT had longer QT intervals than the controls ( $278 \pm 9$  vs  $259 \pm 6$  msec,  $p < .08$ ). Whereas 12 of 20 VT subjects failed to shorten their QT interval by 25% only 5 of 20 controls demonstrated this finding,  $p < .05$ . (Formerly: Complication of Maximal treadmill Exercise in Apparently Normal Subjects)



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00230-03 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 Characters or less. Title must fit on one line between the borders.)

Effect of Aging on  $\text{Ca}^{2+}$  Ion Homeostasis and Neurotransmitter Synthesis and Release

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI R. Hansford

Chief, EMBS

LCS, NIA

Other: F. Castro

Chemist

LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Energy Metabolism and Bioenergetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.9

## PROFESSIONAL:

0.2

## OTHER:

0.7

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

This project is based upon the premise that the homeostasis of  $\text{Ca}^{2+}$  ion concentrations in neuronal tissue may be perturbed in old-age, and that this perturbation may underlie the decreased production and release of the neurotransmitter acetylcholine which has been described in old-age. We have further suggested that a decreased activation by the calcium ion of the enzyme pyruvate dehydrogenase may occur upon depolarization of nerve-terminals from aged animals, and that this may be responsible for decreased production of acetyl-CoA, and thence acetylcholine. Using rat synaptosomes (pinched-off presynaptic nerve endings from cerebral cortex) as a model, we have shown that the synthesis and release of acetylcholine as measured using radiolabelled precursors is indeed decreased in old-age. However, we have this year failed to establish any difference in the degree of activation of pyruvate dehydrogenase upon plasma-membrane depolarization when synaptosomes from 24 month old rats are compared with those from 6 month old animals. In view of the heterogeneity of synaptosomal preparations, and the strong possibility that the age-linked decrement in acetylcholine synthesis and release may only reflect the behavior of a sub-population of synaptosomes, we would regard our experimental results as preliminary results which fail to support the hypothesis outlined above, rather than as requiring the rejection of the hypothesis.

Combined into Z01 AG 00249-01 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00231-03 LCS

## PERIOD COVERED -

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Role of Calcium in the Regulation of Energy Metabolism

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	R. Hansford	Chief, EMBS	LSC, NIA
Others:	F. Castro	Chemist (transferred to CFS, LCS 1/87)	LCS, NIA
	R. Moreno-Sanchez	Visiting Fellow	LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Energy Metabolism and Bioenergetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

0.9

0.8

0.1

## CHECK APPROPRIATE BOX(ES)

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |   |
| <input type="checkbox"/> (a2) Interviews    |  |   |

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project is designed to assess the physiological importance of calcium ions in the regulation of energy metabolism. We have exposed isolated rat cardiac myocytes to a variety of agents and conditions expected to alter cytosolic free calcium ion concentration and have measured the rate of  $O_2$ -uptake by the cell suspensions, as well as the cellular content of NADH. Further, we have estimated cytosolic calcium concentration using fluorescent chelating agents, in parallel experiments performed under identical conditions. In each case, there was a good correlation between the magnitude of the increase in calcium concentration and the degree of stimulation of  $O_2$ -uptake. Attempts were made to assess the quantitative significance of direct activation of respiration by calcium ions at the level of mitochondrial dehydrogenases versus an indirect mechanism involving increased ADP generation. Ruthenium red, which blocks the former process but not the latter, gave a small decrease in rates of  $O_2$ -uptake. However, activation of oxidative phosphorylation by ADP was a predominant mechanism, based on the lowered mitochondrial content of NADH which was observed to occur in response to calcium mobilization.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00232-03 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Age on Hemodynamic and Metabolic Exercise Performance in Normal Man

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: A. Ziemba Visiting Fellow LCP, NIA

R. Andres Chief LCP, NIA

E. G. Lakatta Chief LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

.8

## PROFESSIONAL:

.4

## OTHER:

.4

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Maximal treadmill exercise with measurement of expired gases has been performed in more than 600 clinically normal BLSA volunteers over the past 5 years. Although a formal data analysis is currently in progress, it appears that the strong age-related decline in both maximal heart rate and maximal aerobic capacity ( $VO_{2max}$ ) noted in small BLSA samples will be confirmed. However, age-related changes in  $VO_{2max}$  are attenuated markedly when  $VO_{2max}$  is normalized for muscle mass.

To determine the role of catecholamines in the well known age-related decline in exercise capacity, we measured plasma norepinephrine (NE) and epinephrine (E) at rest and during maximal treadmill exercise in 24 healthy men. Resting NE was not age-related but resting E was higher in men 68-77 years old than in those 22-37 or 44-55 years of age. At maximal effort both NE and E were higher in the elderly men. Furthermore, at submaximal workloads NE and E increased with age, both before and after normalization for relative effort as a percent of peak  $VO_{2max}$ .

In another study, the metabolic effect of relatively prolonged aerobic exercise is being assessed in healthy men.

The relationship of  $VO_{2max}$  to blood lipid levels and blood pressure is being determined in the entire active BLSA population via a multivariate analysis done in collaboration with the Metabolism Section, LCP.

Combined into Z01 AG 00248-01 LCS.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00233-03 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Beta-Adrenergic Modulation of Myocyte Ca<sup>2+</sup>, Membrane Currents, and Contraction

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: H. A. Spurgeon Physiologist LCS, NIA  
 M. C. Capogrossi Senior Staff Fellow LCS, NIA  
 M. D. Stern IPA LCS, NIA  
 R. S. Danziger Medical Staff Fellow LCS, NIA  
 D. J. Peltz Biologist LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.9

## OTHER:

.1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Beta-adrenergic agonists increase the myocardial contraction strength and enhance relaxation. Calcium is a critical agent in the activation and relaxation of contraction in the heart. When calcium binds to the myofilaments, contraction is initiated; when calcium comes off the myofilaments, relaxation occurs. Two possible determinants of relaxation are: (1) the sensitivity of the myofilaments for calcium, and (2) calcium sequestration e.g. by the sarcoplasmic reticulum (SR). The contractile enhancement by beta-adrenergic agonists is due to an increase in the calcium released into the myoplasmic space. Whether beta-adrenergic stimulation specifically abbreviates the cytosolic calcium transient, measured via the calcium indicator aequorin in intact muscle, is controversial. We examined the effect of isoproterenol,  $5 \times 10^{-6}$  M, on cytosolic calcium transient (measured via indo 1 fluorescence 410 nm/490 nm) membrane potential and cell shortening during the twitch (video edge detector) in single rat and guinea pig cardiac myocytes. In guinea pig cells isoproterenol (0.1  $\mu$ M) increased the peak calcium current 3-fold. The 4-fold larger estimated calcium entry (integrated area of calcium current) contributes to the estimated augmentation of contraction. The steady state myoplasmic calcium transient rose with 2.7 fold larger rate to a 2.7 fold higher peak and was reached after 65 instead of 300 ms after the start of depolarization. Isoproterenol accelerated the decay of the calcium transient 4.4 fold. Thus, the beta-adrenergic agonist, isoproterenol, not only potentiates the twitch but also leads to more rapid and complete relaxation of the myoplasmic calcium transient under the present conditions. This may account for the accelerated relaxation of contraction.

(Formerly, Autonomic Modulation of Myocardial Cell Ca<sup>2+</sup>)



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00234-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurotransmitter Modulation of Cardiac Myocyte Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R. S. Danziger Medical Staff Fellow LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA  
 D. J. Pelto Biologist LCS, NIA  
 M. C. Capogrossi Senior Staff Fellow LCS, NIA  
 T. Kaku Visiting Fellow DOD 5/30/86 LCS, NIA  
 C. Filburn Research Chemist LBC, NIA  
 R. G. Hansford Chief, EMBS LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NTA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The adrenergic and cholinergic components of the autonomic nervous system serve an important modulatory role in the cardiovascular system. Norepinephrine is the primary physiologic agonist in the adrenergic arm of the autonomic system. In the heart, norepinephrine is known to activate three types of receptors: alpha 1, alpha 2, and beta 1. The increase in cell calcium by norepinephrine both augments action potential triggered sarcoplasmic reticulum (SR) calcium release to cause an enhanced contractility and increases the likelihood for arrhythmogenic diastolic SR calcium release, seen in myocytes as spontaneous contractile waves. While the positive inotropic effect of alpha<sub>1</sub>-adrenergic agonists on myocardial contractility is thought to be mediated via an increase in cell inositol 1,4,5-tris phosphate (IP<sub>3</sub>), alpha<sub>1</sub>-adrenergic agonists also increase 1,2-diacylglycerol which activates protein kinase C. We examined the relative potency of alpha and beta mechanisms and the effect of phorbol ester, an activator of protein kinase C, on these neurotransmitter effects in single adult rat myocytes. Contractility was measured as the velocity of shortening during stimulation at 1 Hz. Waves were measured in a 30 sec window following 2 min of stimulation. In absence of drugs average velocity of shortening was 70±32 μm/sec (xSEM, n=6) and no waves occurred. Norepinephrine (1x10<sup>-6</sup> M) increased velocity of shortening to 300±70% control (n=6), and caused 3.6±1.55 waves to occur (n=6). Beta (norepinephrine plus prazosin (1x10<sup>-6</sup> M) had a similar effect: velocity of shortening increased to 310±93% control and 1.8±0.95 waves occurred (n=6). In contrast alpha (norepinephrine plus propranolol (1x10<sup>-6</sup> M) increased velocity of shortening by 37±28% (n=6) and no waves occurred. Thus, the increased contractility and enhanced probability for spontaneous diastolic calcium release to occur in response to neurotransmitter release in situ are essentially beta rather than alpha in nature.

Combined into Z01 AG 00233-03 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00235-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

~~Excitation-Contraction Coupling in the Hyperthyroid Heart~~

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	R. Josephson	Medical Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	H. A. Spurgeon	Physiologist	LCS, NIA
	D. J. Felto	Biologist	LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

0.9

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |   |
| <input type="checkbox"/> (a2) Interviews    |  |   |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Hyperthyroidism is known to alter both systolic and diastolic cardiac function, as well as induce left ventricular hypertrophy. To investigate the cellular basis for these phenomena rats were rendered hyperthyroid and single left ventricular myocytes were isolated via collagenase perfusion of the intact heart. Contractile waves in the absence of stimulation as well as stimulated twitches were measured. Isolated hyperthyroid myocytes, when compared to their euthyroid controls, were found to maintain many of the contractile properties found in bulk preparation, thus validating the model and indicating that at least some of the changes in cardiac function seen in the hyperthyroid state are intrinsic to the myocardium, and not secondary to altered loading conditions or heart rate. Using contractile waves in the absence of stimulation as an indication of the frequency of spontaneous calcium-induced calcium release from the sarcoplasmic reticulum, we find that hyperthyroid myocytes have more frequent spontaneous sarcoplasmic reticulum calcium release than euthyroid myocytes. Under some conditions these waves diminish twitch amplitude to a greater extent in hyperthyroid than in euthyroid myocytes. This may provide a basis for the hyperthyroid cardiomyopathy. Hyperthyroid myocytes are also more sensitive to both the inotropic and toxic effects of digitalis glycosides than euthyroid myocytes. Glycoside augmentation of contractile waves and induction of aftercontractions seen in single myocytes may reflect the cellular basis of afterdepolarizations and aftercontractions seen in bulk muscle. Studies are in progress to analyze photomicrographs of hyperthyroid myocytes so that functional changes which we have characterized on the cellular level may be extrapolated to the level of the sarcomere, the fundamental contractile unit.

Discontinued.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00236-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cardiovascular and Metabolic Performance in Highly Trained Older Men

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	D. Drinkwater	Visiting Fellow	LCP, NIA
	J. Busby	Guest Researcher	LCP, NIA
	E. G. Lakatta	Chief	LCS, NIA
	R. Andres	Chief	LCP, NIA

## COOPERATING UNITS (if any)

Johns Hopkins Medical Institutions (A. Goldberg, P. Coon, G. Gerstenblith, S. Fortney)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.5

## PROFESSIONAL:

0.3

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unabbreviated type. Do not exceed the space provided.)

The functional decline in cardiovascular and metabolic reserve which occurs with advancing age may not be solely attributed to biological aging but may derive in part from the increasingly sedentary life style that accompanies aging. To determine the role of physical activity in preserving functional capacity, we have measured body composition, maximal aerobic capacity ( $VO_{2max}$ ), cardiac volumes at rest, during maximal bicycle exercise and lower body negative pressure, blood lipids and glucose tolerance in 19 highly trained men (T) aged 60-76 years. A comparison with 11 healthy lean sedentary controls (C) is shown below.

	T	C	P
Age	65±1	65±2	NS
% body fat	14±1	15±1	NS
$VO_{2max}$ (ml/kg/min)	51±1	30±2	<.01
LDL cholesterol (mg/dl)	117±5	129±10	NS
HDL cholesterol (mg/dl)	59±3	49±3	<.05
Triglycerides	76±4	112±10	NS
Fasting glucose (mg/dl)	93±2	98±2	<.05
2 hr postprandial glucose (mg/dl)	104±6	124±3	<.05
Mean ± SEM			

Thus in older men, high levels of physical activity appear to attenuate age-related declines in cardiovascular and metabolic function.

Combined into Z01 AG 00248-01 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00237-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Prognostic Significance of Specific Electrocardiographic Findings

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg

Staff Cardiologist

LCS, NIA

## COOPERATING UNITS (if any)

Cardiology Division, Medical College of Wisconsin, Milwaukee (D. D. Tresch)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.3

## PROFESSIONAL:

0.3

## OTHER:

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously characterized the long-term prognosis of 24 clinically healthy men with complete right bundle branch block (RBBB), identified from the BLSA population.

Most recently we have characterized the clinical significance and prognosis of sinus bradycardia (SB) <50 beats/min in 47 healthy non endurance trained men older than 40 years. When compared to a control group after a mean follow-up of 5.4 years, the SB group demonstrated a higher prevalence of associated conduction abnormalities (first degree AV block, left axis deviation and complete and incomplete RBBB). 43% versus 19%,  $p < .05$ . On maximal treadmill exercise testing, maximal heart rate did not differ between groups, although exercise duration was greater in the SB group,  $11.0 \pm 2.8$  versus  $9.7 \pm 3.1$  min,  $p < .05$ . None of the subjects with SB developed syncope, high degree AV block, or other manifestations of serious cardiac conduction disturbances during follow-up. Major cardiac events (angina pectoris, myocardial infarction, congestive heart failure or cardiac death) occurred in 8% of the SB group and 11% of controls over the 5.4 year mean observation period.

Combined into Z01 AG 00228-04 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00238-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Exercise-induced Arrhythmias in Diuretic-Treated Subjects with Hypertension

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others: E. G. Lakatta, Chief LCS, NIA

## COOPERATING UNITS (if any)

Department of Anesthesiology, Yale University School of Medicine (G. Bause)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.4

## PROFESSIONAL:

0.3

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Major controversy has recently arisen regarding a possible increased incidence of sudden cardiac death in hypertensive individuals treated with diuretics. To investigate a possible etiologic mechanism for such an outcome, we compared the prevalence and complexity of exercise-induced arrhythmias in BLSA subjects on chronic diuretic monotherapy for untreated hypertension with that in normotensive control group. Although the prevalence of exercise induced arrhythmias was higher in the diuretic treated group (D) than in controls (C) 57% versus 38%,  $p < .05$ , this difference was due entirely to the higher prevalence of simple ventricular ectopic beats (VEB) 44% versus 26%,  $p < .05$ . No difference between the groups was found in the prevalence of frequent or complex ectopic beats. Furthermore, within the D group, no difference in the occurrence of ectopic beats was found between men and women, those with resting ECG abnormalities and those without or between those with serum K  $< 3.7$  versus those with higher serum K.

Combined into Z01 AG 00228-04 LCS





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00239-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structure and Function of Single Cardiac Myocytes Over a Broad Age Range

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	H. A. Spurgeon	Physiologist	LCS, NIA
Others:	R. Josephson	Medical Staff Fellow	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA
	M. Sakai	Visiting Fellow	LCS, NIA
	R. S. Danziger	Medical Staff Fellow	LCS, NIA
	D. J. Peltz	Biologist	LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

1.4

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There has been considerable prior work from this laboratory as well as others documenting that the time course of cardiac contraction in bulk muscle is prolonged with aging. Common measures of inotropy such as the maximal rate or amplitude of tension development appear unchanged with age. However, alterations in the cardiovascular response to stress occur with aging and have been attributed, in part, to a diminished effect of autonomic modulation of cardiovascular function. Whether these measurements represent fundamental characteristics of aging cells or are a reflection of an altered cellular composition of bulk muscle is unclear. Furthermore, what aging-associated alterations, if any, characterize the contractile properties of the fundamental contractile unit, the sarcomere, are unknown. We therefore measured the maximal velocity, amplitude, and time course of unloaded contractions of single isolated cardiac myocytes obtained from rates 2, 8, and 24 months old. We also combined these measurements with data on cell and sarcomere lengths which we have previously determined in similar cells. We find that the prolongation of the time course of contraction that occurs with aging is a fundamental property of the myocyte and must reflect changes in the basic processes governing excitation-contraction coupling. The maximal rate or extent of shortening of individual sarcomeres is unaltered with aging, and the series addition of sarcomeres (which we have previously shown to characterize the aging heart) appears to be an adaptation that may permit the aging heart to meet the challenge of the increased load against which it must function. A decreased contractile response to norepinephrine with adult aging can also be demonstrated directly in cardiac myocytes. This deficit may be specific to catecholamines since the response to a non-adrenergic calcium channel agonist, BayK, is not age-related.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00240-02 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Mechanisms of Abnormal Automaticity in Cardiac Preparations

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. C. Capogrossi	Senior Staff Fellow	LCS, NIA
Others:	E. G. Lakatta	Chief	LCS, NIA
	A. Talo	Visiting Scientist	LCS, NIA
	D. J. Pelto	Biologist	LCS, NIA

## COOPERATING UNITS (if any)

Department of Physiology, Temple University, Philadelphia, PA (S. R. Houser and A. Bahinski)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

While resting mammalian ventricular myocardium does not usually exhibit pacemaker like activity, under certain conditions spontaneous localized release of  $Ca^{2+}$  from sarcoplasmic reticulum (SR) results in an increase in myoplasmic  $[Ca^{2+}]$  ( $Ca_i$ ) which causes miniature inward currents resulting in oscillations of membrane potential. At the normal resting membrane potential in cardiac myocytes this is insufficient to induce an action potential. However, when spontaneous SR  $Ca^{2+}$  release occurs simultaneously at more than a single locus, i.e. when these loci are "synchronized," the resultant sarcolemmal depolarization is augmented to levels that are sometimes sufficient to produce a spontaneous action potential and contraction. Thus, multiple areas of localized spontaneous  $Ca^{2+}$  release within ventricular cardiac cells, if "synchronized" is a mechanism for abnormal automaticity in these cells and can produce a "heart beat in reverse."

Combined into Z01 AG 00243-01 LCS.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00243-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pathophysiological Effects of Spontaneous  $\text{Ca}^{2+}$  Release in the Heart

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: M. C. Capogrossi Senior Staff Fellow LCS, NIA

Others: E. G. Lakatta Chief LCS, NIA  
 M. D. Stern IPA LCS, NIA  
 H. A. Spurgeon Physiologist LCS, NIA  
 D. J. Peltó Biologist LCS, NIA  
 R. Weiss Medical Staff Fellow LCS, NIA

## COOPERATING UNITS (If any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.5

## PROFESSIONAL:

2.2

## OTHER:

0.3

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

All mammalian cardiac preparations, given sufficient  $\text{Ca}^{2+}$  loading, exhibit spontaneous release of  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (SR). Videomicroscopy in muscle and myocytes has shown that the myofilament motion due to this type of  $\text{Ca}^{2+}$  release is (1) spatially non-uniform and (2) propagates at approximately 100  $\mu\text{m}$  sec as a contractile wave, indicating that the spontaneous  $\text{Ca}^{2+}$  release occurs locally, and, in diffusing down its concentration gradient, causes a regenerative  $\text{Ca}^{2+}$  induced  $\text{Ca}^{2+}$  release from the SR. The localized  $[\text{Ca}^{2+}]$  achieved as result of spontaneous SR release has been estimated to range from a few  $\mu\text{M}$  to 40  $\mu\text{M}$ . Myofilaments in areas of high  $\text{Ca}^{2+}$  shorten and stretch neighboring myofilaments where  $[\text{Ca}^{2+}]$  is lower. Since, in bulk cardiac tissue this occurs asynchronously among cells, quiescent cells are stretched and therefore sarcomere loading in these cells is affected. The net result of these events is  $\text{Ca}^{2+}$ -dependent diastolic tonus. The diastolic oscillatory  $\text{Ca}^{2+}$  modulation of sarcolemmal ion conductances within areas of high  $\text{Ca}_i$  results in sarcolemmal depolarization, which, if sufficient in magnitude, triggers a spontaneous action potential and leads to arrhythmias. Finally, the resultant inhomogeneity in the extent of SR  $\text{Ca}^{2+}$  loading and phases of SR  $\text{Ca}^{2+}$  recycling that occur in the presence of spontaneous SR  $\text{Ca}^{2+}$  release cause a reduction in the net extent and synchrony of systolic  $\text{Ca}^{2+}$  release from the SR by a subsequent action potential. This impairs systolic function. Enhanced diastolic tone, the occurrence of arrhythmias, and compromised systolic function are cardinal signs of many myocardial disease states. The conceptualization of spontaneous SR  $\text{Ca}^{2+}$  release as interpreted and discussed in the context of the present findings in cardiac myocytes, though speculative in some regard, provides a logical framework in which no structure testable hypotheses about its potential role in the pathophysiology of some forms of heart disease.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00244-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Myocardial Calcium Oscillations During Reperfusion and Reoxygenation

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. G. Lakatta	Chief	LCS, NIA
Others:	R. G. Weiss	Medical Staff Fellow	LCS, NIA
	M. D. Stern	IPA	LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Medical Institutions (G. Gerstenblith)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.5

## PROFESSIONAL:

1.3

## OTHER:

.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The full extent of myocardial contractile recovery following ischemia is delayed beyond the immediate reperfusion (R). This may be associated with delayed metabolic recovery and/or  $\text{Ca}^{2+}$  overload. This can be quantified in the beating heart by the scattered laser intensity fluctuations (SLIF) which senses Ca oscillations (CaOs) it produces. We measured ATP, and pH by  $^{31}\text{P}$  NMR and SLIF, and developed pressure in isovolumic rat hearts. During the first 5 min of R there is rapid metabolic but a more gradual developed pressure and SLIF recovery. Then both gradually recover developed pressure abruptly and SLIF increases fourfold over the next 40 min mean no change in metabolic parameters. These findings suggest that delayed contractile recovery during R is attributable in part to an adverse effect of increased CaOs induced by  $\text{Ca}^{2+}$  overload during R. In additional hearts, For the first 10 min of R, perfusate Ca was 1.5mM (Group 1, n=4) or 0.08mM (Group 2, n=4). During R the early peak in SLIF was not present in Group 2. Recovery of DP was higher and cell Ca lower in Group 2 vs Group 1 at 20 min R. Thus, CaOsc during early R are modified by perfusate Ca, noninvasively index the extent of Ca loading, and predict functional recovery.

Other hearts were pretreated with Amiloride  $10^{-4}$ , a known Na-Ca blocker during hypoxia and reoxygenation ( $\text{ReO}_2$ ). During  $\text{ReO}_2$ , DP, EDP and PCr (all % baseline), and  $\text{pH}_i$  recovery were improved in the Amiloride treated hearts. Cell gain during  $\text{ReO}_2$  was reduced 50% by Amiloride. These results suggest that cell Ca loading during reoxygenation is Na dependent and may be mediated in part by Na/Ca exchange.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00245-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cardiac Muscle Properties in Senescent Rats is not Related to Serum Urea Levels

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E. G. Lakatta Chief LCS, NIA

Others: H. A. Spurgeon Physiologist LCS, NIA

## COOPERATING UNITS (If any)

Division of Cardiology, Johns Hopkins Medical Institutions (G. Gerstenblith)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.3

## PROFESSIONAL:

.25

## OTHER:

.05

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

One of the most striking changes in the cardiovascular system which accompanies advancing age is the prolongation of the duration of systole. This age-associated prolongation occurs in man, lower mammals, and in rodents, and apparently represents an age related change in cardiac muscle across species. However, advancing age in rodents is also often accompanied by a progressive decline in renal function, making it difficult to partition cardiovascular changes into truly age-related versus renal related declines. In order to determine whether myocardial function in senescent (24 mo) male Wistar rats varies with SUN, we measured function of isolated cardiac muscle from animals with higher and lower SUN. Muscles were bathed in normal Ringer's bicarbonate solution ( $[Ca] = 1.0 \text{ mM}$ ) and stimulated to contract  $24 \text{ min}^{-1}$  at  $30^\circ\text{C}$  at  $L_{\text{max}}$ . The mean  $\pm$  SEM, SUN, resting tension (RT), developed twitch tension (TT), maximum rate of tension rise ( $dt/dt_{\text{max}}$ ) and contraction duration (CD) in the two groups were:

SUN	p<.000	N	RT (g/mm <sup>2</sup> )	TT (g/mm <sup>2</sup> )	dt/dt (g/mm <sup>2</sup> /max sec)	CD (msec)
60.83 $\pm$ 2.31		6	1.46 $\pm$ .28	3.19 $\pm$ .46	35.45 $\pm$ 4.88	283 $\pm$ 7
26.14 $\pm$ 1.44		7	1.45 $\pm$ .42	3.23 $\pm$ .64	36.74 $\pm$ 7.96	290 $\pm$ 8

Thus, these contractile properties of isolated cardiac muscle do not depend on SUN. Additionally, the maximum contractile response to isoproterenol ( $10^{-5}\text{M}$ ) did not vary with SUN ( $dt/dt = 34\pm 6$  vs  $21\pm 9\%$  control in the high and low SUN group respectively). We conclude that contractile function in cardiac muscle from senescent rats is not affected by the levels of SUN encountered in these rats.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00246-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Alpha-Adrenergic Stimulation on Isolated Ventricular Myocytes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: W. A. Kachadorian Staff Scientist LCS, NIA

Others: M. C. Capogrossi Senior Staff Fellow LCS, NIA

E. G. Lakatta Chief LCS, NIA

H. A. Spurgeon Physiologist LCS, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

1

.9

.1

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Alpha-adrenergic stimulation is known to lead to the formation of at least two second messengers, inositol trisphosphate ( $IP_3$ ) which is thought to release  $Ca^{2+}$  from the sarcoplasmic reticulum (SR) and 1,2 diacylglycerol (DAG) which activates a  $Ca^{2+}$ -dependent protein kinase, i.e. protein kinase C (PKC). Previous work done in our laboratory showed that both DAG and the tumor promoting agent phorbol ester increase membrane activation of PKC and have a negative inotropic effect in adult cardiac myocytes. We hypothesized that because of its  $Ca^{2+}$ -dependence that during high cell  $Ca^{2+}$  loading PKC activation would be more marked than under normal cell  $Ca^{2+}$  loading and possibly determine a negative inotropic effect of alpha-adrenergic stimulation rather than the better known positive response which could be related to the action of  $IP_3$  to release  $Ca^{2+}$  from the SR.

Isolated rat ventricular myocytes, pretreated with propranolol were used to investigate the effect of alpha-adrenergic stimulation with phenylephrine on the frequency of spontaneous contractile waves (CW), which represent the mechanical expression of spontaneous  $Ca^{2+}$  release from the SR, and on twitch amplitude (TA). CW were measured in the unstimulated state and TA was determined during field stimulation. a. In the absence of stimulation, in 5 mM  $Ca^{2+}$  treatment with phenylephrine led to a significant reduction in CW frequency and this was reversible upon removal of the drug. b. In cells stimulated to contract at a rate of 0.2 Hz, in 5 mM  $Ca^{2+}$  CW appeared in some of the diastolic intervals. Treatment with phenylephrine caused abolition of diastolic CW and a significant diminution in TA. This negative effect of phenylephrine was in contrast to a positive inotropic action observed in parallel studies in 1 mM  $Ca^{2+}$ . These findings are consistent with the view that the effect of alpha-adrenergic stimulation of cardiac cells can vary in relation to intracellular  $[Ca^{2+}]$ .



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00247-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Detection and Prognosis of Silent Myocardial Ischemia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. L. Fleg	Staff Cardiologist	LCS, NIA
Others:	A. Zondermen	Senior Staff Fellow	LPC, NIA
	P. Costa	Chief	LPC, NIA
	R. Josephson	Medical Staff Fellow	LCS, NIA
	E. G. Lakatta	Chief	LCS, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital (G. Gerstenblith, S. Gottlieb, L. Becker, and M. L. Weisfeldt)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.0

## PROFESSIONAL:

0.8

## OTHER:

1.2

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To ascertain whether the addition of exercise thallium scintigraphy (TS) to standard exercise electrocardiography (ECG) would enhance the prediction of future cardiac events in clinically healthy subjects, we performed both ECG and TS with maximal treadmill exercise in 409 volunteers (aged 40-92 yr) from the BLSA who were free of cardiac disease by history, physical examination, and resting ECG. Over a mean followup interval of 4.6 yr, 42 coronary events were recorded. The predictive value for a coronary event in the 23 subjects with both ischemic ECG and abnormal TS was 48%. By logistic regression analysis, the combination of ischemic ECG and abnormal TS predicted a 6.3 fold relative risk of a subsequent coronary event, independent of conventional risk factors (age, sex, smoking status, hypertension, total cholesterol). Thus, the combination of ischemic ECG and abnormal TS in totally asymptomatic subjects is a potent predictor of future coronary events.

Among 696 apparently healthy subjects from the BLSA who have undergone serial maximal exercise treadmill testing since 1977, the risk of subsequent cardiac events was compared in those whose initial test was positive (Group I) versus those converting from a negative to a positive test (Group II) over a 5.7 yr mean followup.

	Group I	Group II
n	70	80
age	64	62
men (%)	54*	86
events	11	9
events/yr (%)	2.6	2.1

\*p&lt;.01 by Chi square analysis

Thus in asymptomatic subjects, serial conversion from a negative to a positive exercise ECG is of no greater predictive value for a future coronary event than an initially positive response.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00248-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Factors Determining Maximal exercise performance in man

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: J. L. Fleg Staff Cardiologist LCS, NIA

Others:	E. G. Lakatta	Chief,	LCS, NIA
	J. Busby	Guest Researcher	LCP, NIA
	D. Drinkwater	Visiting Fellow	LCP, NIA
	R. Andres	Chief	LCP, NIA
	L. Fried	IPA	LCP, NIA
	J. Tobin	Chief, APS	LCP, NIA

## COOPERATING UNITS (if any)

Division of Cardiology, Johns Hopkins Hospital (G. Gerstenblith, L. Becker, M. L. Weisfeldt); School of Hygiene, Johns Hopkins Hospital (S. Fortney); GCRC (A. Goldberg)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Cardiac Function Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

1.8

2.4

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Maximal oxygen consumption ( $VO_{2max}$ ) during treadmill exercise has been performed in nearly 700 BLSA volunteers over the past 7 years. In a carefully selected nonobese group of 83 men and 101 women without exercise-induced ischemia,  $VO_{2max}$  expressed in ml/kg body weight/min declined sharply with age (men:  $VO_{2max} = 54.9 - 0.39 \text{ age}$ ,  $r^2 = .60$ ; women:  $VO_{2max} = 41.0 - 0.25 \text{ age}$ ,  $r^2 = .50$ , both  $p < .0001$ ). After normalization for 24 hour urinary creatinine excretion, an index of total body muscle mass, the age decline in  $VO_{2max}$  was markedly attenuated in both sexes (men:  $r^2 = .14$ , women:  $r^2 = .08$ ). To determine the role of physical activity in preserving functional capacity with advancing age, we have measured  $VO_{2max}$ , body composition, blood lipid, glucose tolerance, and cardiac volumes at rest, during maximal treadmill exercise in 19 highly trained men 60-76 years old. Whereas  $VO_{2max}$  ( $51 \pm 1$  versus  $30 \pm 2$  and HDL cholesterol ( $59 \pm 3$  versus  $49 \pm 3$ ) were significantly higher than in age matched nonathletic controls, plasma LDL, fasting and 2 hr postcardiac glucose were lower. Preliminary data during upright bicycle exercise suggest that both L ventricular end diastolic volume and stroke volume are greater and heart rate lower at any submaximal load than in control subjects.

The metabolic effects of relatively prolonged submaximal treadmill exercise is being studied in normal BLSA men. Preliminary results suggest a significant age-related augmentation of plasma catecholamines after 45-60 min of exercise, similar to that previously found in BLSA men during short-term maximal treadmill testing. The response to maximal upright bicycle exercise in over 30 BLSA subjects with exercise-induced myocardial ischemia detected by ECG or thallium scan is being compared with that of age-related nonischemic BLSA controls. Gender differences in the hemodynamic response to bicycle exercise are also being explored.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00249-01 LCS

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (90 characters or less. Title must fit on one line between the borders.)

Cellular  $Ca^{2+}$  Ion Homeostasis and the Impact of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	R. G. Hansford	Chief, EMBS	LCS, NIA
Others:	F. Castro	Chemist (transferred to CFS, LCS 1/87)	LCS, NIA
	J. Staddon	Visiting Fellow	LCS, NIA
	R. Moreno-Sanchez	Visiting Fellow	LCS, NIA

## COOPERATING UNITS (if any)

Cardiac Function Section, LCS

## LAB/BRANCH

Gerontology Research Center, Laboratory of Cardiovascular Science

## SECTION

Energy Metabolism and Bioenergetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.4

## PROFESSIONAL:

2.2

## OTHER:

0.2

## CHECK APPROPRIATE BOXES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project constitutes an investigation into mechanisms whereby cells achieve the homeostasis of cytosolic free  $Ca^{2+}$  concentrations ( $[Ca^{2+}]_c$ ), and allow perturbations in  $[Ca^{2+}]_c$  in response to hormones and neurotransmitters. Further, it addresses derangements in these control mechanisms which may occur in old-age. This year, we have asked the following questions. (1) What is the mechanism whereby the hormone glucagon leads to an increase in  $[Ca^{2+}]_c$  in hepatocytes? The efficacy of cyclic-AMP analogues in raising  $[Ca^{2+}]_c$  and the similar dose-response to glucagon of changes in  $[Ca^{2+}]_c$  and changes in the activity of pyruvate kinase, which is phosphorylated by protein kinase A, have suggested to us that a mechanism involving solely protein kinase A is sufficient, though other mechanisms cannot be excluded. (2) What membrane carrier proteins are involved in mediating the entry of  $Ca^{2+}$  into myocytes when they are treated with veratridine? This compound potentiates Na<sup>+</sup>-channel activity and leads to a large increase in  $[Ca^{2+}]_c$ , an effect which we have found to be a useful tool in simulating a high work-load for our metabolic studies in myocytes. We have sought to distinguish between an involvement of  $Ca^{2+}$  channels and Na<sup>+</sup>/Ca<sup>2+</sup> exchange by using the inhibitors verapamil, nitrendipine, Cd<sup>2+</sup> and dichlorobenzamil, and have obtained answers indicating that the contribution of these two processes to total flux varies with the extracellular Na<sup>+</sup>, H<sup>+</sup> and Ca<sup>2+</sup> concentrations and the degree of depolarization. (3) Are there distinct alpha- and beta-adrenergic effects on the depolarization-induced entry of  $Ca^{2+}$  into cardiac myocytes? We have studied cells loaded with Quin-2 and have identified a novel interaction, such that  $Ca^{2+}$  flux is activated more by beta-agonists alone than by alpha- and beta-agonists together. (4) Are there correlates at the level of protein phosphorylation of the previously described decreased responsiveness of  $Ca^{2+}$  transport to catecholamines in the aging heart? We have identified a decreased phosphorylation of troponin in myocytes from senescent rats and are currently focusing on phospholamban.



# Annual Report of the Laboratory of Cellular & Molecular Biology

## National Institute on Aging

### Inorganic Biochemistry Section

The Inorganic Biochemistry Section has made considerable progress in studies on the mechanism of RNA synthesis, the importance of conformational changes in DNA, and in the development of techniques for the in vivo study of aging in humans and animals by NMR.

Active Site of RNA Polymerase. We are determining the spatial relationship between the two substrates that are brought together by RNA polymerase to form the internucleotide bonds required for RNA synthesis. In accordance with a proposal by Yager and Von Hippel we now call the initiation and elongation sites  $i$  and  $i + 1$  sites. We have previously reported the distance between the metals in  $i$  and  $i + 1$ , Zn(II) and Mg(II) to be 5.2 Å, when both metals were substituted by the paramagnetic Mn(II). This distance was determined in the absence of substrates and DNA template. The next step in our plan was to determine these distances in the presence of substrate both in the absence and presence of template. These objectives were accomplished by observation of the paramagnetic effect of Mn(II) in  $i$  on the EPR spectra of Mn(II) in  $i + 1$ , using NMR techniques for determining the electron spin relaxation time of the perturbing paramagnetic center Mn(II) in  $i$ . The distance between the metals in the presence of ATP substrate in  $i$  and  $i + 1$  was calculated to be 6.0 Å in the absence of template and 6.7 Å after the addition of polydAdT·polydAdT template. Within the 10% error in the measurement of these distances no significant change seems to occur in the active site upon addition of substrate, but the addition of the template does appear to evoke such a change. The existence of such a change was confirmed from the major change in the line shape of the EPR spectrum of Mn in the  $i + 1$  site in the presence and absence of template. These results indicate that the introduction of the template significantly alters the active site structure of the enzyme. The binding of the enzyme to the DNA increases the size of the substrate cavity.

Active and Inactive Forms of RNA Polymerase. Even though the RNA polymerase enzyme from *E. coli* has been known for 25 years, the complexity of the enzyme has prevented scientists from understanding aspects of the enzyme that one would have expected to be solved long ago. One of these is the fact that 100% pure enzyme, as determined by protein homogeneity, is not 100% active. The question arises whether there are fully inactive molecules in this "pure" enzyme, and, if so, whether these can be separated from the active molecules.

We wanted to investigate this problem and decided that the best way to differentiate between active and inactive forms would be to allow the enzyme to bind DNA, to allow RNA synthesis to proceed, and to determine whether some molecules would be firmly bound to DNA in a way that supports RNA elongation, while others would be more loosely bound and not have the capacity to support elongation. Then, by temporarily halting RNA synthesis, the loosely bound RNA polymerase could be selectively extracted onto matrix-attached heparin. We have



carried out such extractions, and then restarted the RNA synthesis activity and found RNA synthesis largely restored, in spite of the removal of a large portion of the total enzyme. We consider this result as evidence that pure RNA polymerase contains inactive molecules, and the method for obtaining the evidence could be a method of separation of active and inactive enzymes.

Metals, Cells and Aging. Studies on the metal content of aging human diploid fibroblasts have shown that there is a steady accumulation with increasing in vitro age. We have initiated an examination of the subcellular distribution of the age related metal increase of several metals (Zn, Cu, Mn). Studies to date indicate in vitro aging leads to a much higher accumulation of zinc in the cell nucleus than in the cytoplasm. When the cells are challenged with toxic zinc levels, most of the zinc again penetrates the nucleus. Probably the greater effect on the nucleus is due to a higher permeability of the nucleus to the metal ions.

Human Exercise - Development of Protocols for Aging Studies: The decline in PCr and the increase in  $P_i$  during isometric exercise at 30% of maximum was most rapid during the first 60 seconds. Thereafter, the metabolite concentrations did not change significantly, while the intracellular pH continued to decline for 3 minutes in most cases. A second exercise period following a 3-minute rest period showed metabolite levels similar to those during the first exercise period, but in some cases, showed lower intracellular pH. The metabolites recovered rapidly during 3 minutes of rest and returned to resting levels at the end of the 3-minute period. The intracellular pH also returned to normal in 3 minutes, although its recovery was slow in the early stages of the rest period.

During dynamic exercise at maximum capacity (intermittently every 5 seconds for 3 minutes) similar changes in metabolite levels were observed. However, some individuals showed a smaller change in pH during dynamic exercise compared to isometric exercise. Thus individual differences were more apparent in the response of pH to exercise than that of metabolites. It may be interesting to investigate whether the pH response is age-dependent.

Although both isometric and dynamic protocols produced similar metabolic effects, the former caused more fatigue. Thus it is obvious that there is a component of fatigue that is independent of metabolite levels or pH. Further studies may shed some light on the mechanism of fatigue.

#### Molecular Dynamics Section

The Leakage of Superoxide from Erythrocytes Under Hypoxic Stress. Studies of the rate of oxidation of hemoglobin as a function of oxygen pressure indicates an increased rate of oxidation as the oxygen pressure is lowered, with maximal rates of oxidation in the region of 2 mmHg. Autoxidation of hemoglobin coincides with the formation of superoxide radicals. Studies with intact cells indicate that the cellular superoxide dismutase is not able to react with the excessive superoxide generated under hypoxic stress. This-superoxide is able to leak out of the erythrocyte as indicated by superoxide specific reduction of cytochrome C. These results suggest that hypoxic erythrocytes may be a source of cellular and tissue free radical damage.





Ligand Interactions in Hemoglobin. The coordination site of oxygen and other ligands on hemoglobin is located in a closed ligand pocket. Ligand interactions on hemoglobin can thus be separated into three processes: i) the diffusion of the ligand into the pocket through the globin matrix; ii) the coordination of the ligand already in the pocket to the iron; and iii) globin interactions with the bound ligand. We have been able to delineate important aspects of all three processes by combining various spectroscopic probes with a new freeze quenching technique. This methodology permits us to stop the ligand binding reaction at a specified time subsequent to mixing. Intermediate states are then probed by continuing the reaction at various sub-zero temperatures where intermediate states are stabilized. We elaborate on the first two processes.

Coordination of the Distal Histidine Facilitates Diffusion through the Globin Matrix. Incubation at 233 K results in the formation of a stable complex with the distal histidine. The prior formation of this complex produces a dramatic increase in the rate for the reaction of fluoride with methemoglobin in a frozen sample at 255 K. Surprisingly, instead of competing with the exogenous ligand for the iron, this coordination with the intrinsic distal histidine actually facilitates the uptake of ligands, presumably due to globin conformational rearrangements that open a channel for ligand entry into the pocket.

This mechanism may be of major importance since our results indicate, that even under normal physiological conditions, coordination with the distal histidine does take place to a limited extent. Furthermore, these interactions are facilitated by membrane interactions on the cytoplasmic surface of the erythrocyte.

An Intermediate Hemoglobin State with the Exogenous Ligand Already in the Ligand Pocket but not Strongly Coordinated to the Iron. We find that within a fraction of a second subsequent to mixing, fluoride is associated with hemoglobin, but not yet coordinated to the iron. This fluoride is able to coordinate with iron by incubation at 233 K in the frozen state. Additional studies with oxyhemoglobin at low oxygen pressure indicate that an analogous state, with the oxygen in the pocket but only weakly coordinated to the iron, is responsible for enhanced oxidation of the heme and may represent an important initial stage in the oxygen binding reaction.

The Enhanced Expression of a Specific Form of Cytochrome P-450 in Aged Rats. The cytochrome P-450's are an important class of heme proteins which utilize oxygen to metabolize lipid soluble substances. In collaboration with Fred Friedman of the Laboratory of Molecular Carcinogenesis, NCI, we have previously found an unexpected age-induced increase in the activity of the cytochrome P-450 isoenzyme associated with the hydroxylation of testosterone at the 7 position from  $0.19 \pm 0.01$  at 3 months to  $0.37 \pm 0.03$  at 24 months ( $p < 0.001$ ). Such a change in activity can be due to a number of factors. We have now shown that this increased activity coincides with an increase in the concentration of this isoenzyme as well as the messenger RNA which codes for it. The increased activity thus reflects enhanced genetic expression.

#### Macromolecular Chemistry Section

Alpha-One Adrenoceptors. After the synthesis and evaluation of about forty derivatives of prazosin a useful probe for alpha-one adrenoceptors, alkylating prazosin, was developed. The probe alkylates and thus destroys the sensitivity



of that receptor to hormones and may be of great use, when means are available to do so, to address the interrelation of this signal system and of the neurological problems accompanying aging. Presently, using tissues from young rats which are available, Dr. Kusiak has established that alkylating prazosin binds to all the alpha-one adrenoceptors, but reacts irreversibly with only a fraction of these. This suggests that this receptor type will have to be divided into sub-types.

Beta Adrenoceptors. The regulatory system of which the beta-adrenoceptor is a part is changed in a number of diseases and thus is the target of therapeutic interventions. In our previous work we mainly designed and used probes of the antagonistic type, i.e., derived from beta-blockers. These studies could yield only part of the picture: activation processes are necessarily quite different from a simple blockade. Both we and others were frustrated in attempts to make good agonistic probes; catecholamines, which are natural agonists, are by their instability and reactivity frustrating to both chemists and pharmacologists. Presently, in collaboration with Dr. S.P. Baker (University of Florida), new analogs of catecholamines based on carbostyryl were designed. A few compounds of this type were prepared in the Section and tested at the University of Florida. These tests revealed that pure and potent agonistic activity of the catecholamines could be elicited from the carbostyryl compounds which have good chemical stability and the potential for further synthetic manipulation.

Testosterone. The majority of the time, the circulatory levels of testosterone in young male mammals stay about constant, but during episodic testosterone release these levels increase several times. Episodes last only one-two hours and occur about daily at irregular intervals. The relative importance of base-line levels and episodic levels of the hormone could not be well addressed previously since after the injection of traditional testosterone preparation the levels of hormone did not decrease as rapidly as after the episodes. The pharmaceutical preparation of testosterone developed in the Section enabled us to address the problem. Androgen-sensitive behavior and physiology of castrated rats, after daily supplements of the new preparation, were evaluated in a study by Dr. G.T. Taylor and his collaborators at the University of Missouri. Through the means of a parallel study, it was established that this type of treatment left the rats for at least three quarters of the day on levels of testosterone in the serum which were typical for castrates. Nevertheless, there was a considerable correction of androgen-sensitive behavior and physiology. By administration of the same preparation to intact rats the androgen-sensitive characteristics were boosted above normal levels; interestingly, the muscle weight of the rats increased without exercise.

Presently, hypogonadal men, the majority of which are in advanced age, are supplemented by testosterone using a preparation designed to give constant levels of hormone in the blood. The present results suggest that there is little sense in stressing the need for constant testosterone levels and that natural variation should be imitated in therapy.

Dopaminergic action during aging. We have continued to elucidate the relationship between changes in dopaminergic control of motor function and dopamine receptor loss during aging by various interventions in rats including prolactin, estrogen, and neuroleptic treatment, dietary restriction and



irreversible receptor blockade. Although loss of striatal D<sub>2</sub> receptors with age results in impaired motor control, it appears to be possible to dissociate changes in receptors and response by some of the above manipulators. Moreover, in the pituitary, we have shown that no changes in dopamine receptors occur during aging and a loss of sensitivity for inhibition of prolactin release is due to a post-receptor defect.

From a mechanistic standpoint, we are on the verge of distinguishing between loss of receptor containing neurons and impaired gene expression as a cause of receptor loss during aging. Attempts to generate monoclonal antibodies against purified D<sub>2</sub> receptors have yielded 3 mildly positive clones. These are currently being further tested and propagated for possible future use in obtaining the receptor cDNA from brain gene libraries. This cDNA could then be used for direct examination of possible age changes in receptor gene expression. On the other hand, we have successfully labeled striatal sections in vitro with <sup>3</sup>H-spiperone and have categorized various regions on the basis of D<sub>2</sub> receptor density. Neurons in these regions are currently being quantitated as a function of age to determine whether cell loss alone is of sufficient magnitude to account for the 25-40% loss of receptors during aging.

Finally, we have begun to examine age changes in cholinergic regulation of striatal dopamine release which are also related to changes in control of motor function. Some cholinergic agents work through the inositol phosphate-calcium mobilization system, and some parallels with the aged alpha adrenergic stimulated parotid and LHRH stimulated pituitary cell systems have been observed (see below).

#### Molecular Physiology and Genetics Section

Regulation of calcium mobilization during aging. We have traced age related deficits in calcium dependent processes in the rat parotid gland to defects in the mobilization of this ion from intracellular storage sites. We are currently determining whether such impairment is due to reduced stores of mobilizable calcium or a defect in the inositol trisphosphate receptor which has been postulated to be required for calcium release. Studies with the fluorescent dye, Quin 2, suggest the impairment is not restricted to the alpha adrenergic system, but may involve cholinergic regulation to a lesser extent. On the other hand, parathyroid hormone stimulated calcium release exhibits a totally different pattern during aging and is probably not related to the former processes, both which proceed through the inositol trisphosphate cascade.

Similar studies of age related impairments in calcium mobilization mediated through the inositol trisphosphate mechanism are currently underway in the pituitary (LHRH stimulation) and the striatum (cholinergic stimulation). As in the parotid, defects in the latter systems are at least partially reversible if sufficient calcium can be forced into the cytoplasm of the aged cells.

Effects of Aging on Sensori-Motor Performance in Rodents. A parametric study was conducted using the rotodrum apparatus to assess the effects of aging on maximum running speed in male C57BL/6J mice. The results indicated about a 24% decline in this parameter between 8 and 28 mo of age. The task appeared to be highly reliable as individual differences in performance were stable and further training did not improve performance.





The new paradigm was then included in a battery of psychomotor tests (exploratory activity, inclined screen, tightrope, rotorod, and runwheel) to determine its correlation with other measures of motor aging. In addition, in collaboration with Drs. Roth and Kochman, striatal dopamine receptors were examined in these mice and correlated with motor performance. In a cross-sectional study involving mice aged 8, 18, and 28 mo of age, significant age-related decline was observed in dopamine receptors (23%) which paralleled age-related declines in all the psychomotor tests except exploratory activity and inclined screen. The results of a factor analysis of the variables indicated that age was associated to a dimension that included loss of dopamine receptors as well as declines in rotorod and tightrope performance, wheel activity, and maximum running speed. Within any age group, however, individual differences in dopamine receptor concentrations did not appear to be reliably correlated to individual differences in motor performance in any test.

Effects of Aging on Learning/Memory Function in Rodents. The integrity of the septo-hippocampal cholinergic system was identified as a possible major factor in efficient maze performance that might underlie the age-related impairment observed in this task. Electrolytic lesions made to the fimbria-fornix of young male F-344 rats resulted in deficient maze acquisition, which appeared to mimic the age-related impairment. Not only did the lesioned rats make more errors than young controls, they also appeared to make the type of perseverative errors exhibited by aged rats in this task, retention performance measured 2-3 weeks was also moderately impaired. However, if the lesion was made 1 week after acquisition training, no significant retention impairment was noted 2-3 weeks later. These findings indicate that the septo-hippocampal system is involved in the storage and consolidation of memory for this task, but that long-term memory for this type of striatal and neocortical lesions on retention of maze performance.

Environmental/Nutritional Modulation of Aging in Rodents. In collaboration with Dr. Bresnahan, we are completing a study to determine the interaction of dietary restriction and environmental stimulation on survival and biomarkers of aging in male C57BL/6J mice. The objective is to determine whether the effects of dietary restriction and environmental stimulation act additively on various parameters of aging. Results continue to demonstrate that mice housed in enriched environments ate more food and grew in body weight faster than conventionally reared mice. Within any environmental group, diet-restricted mice weighed about 20% less than ad libitum fed groups. When tested about 26 mo of age, mice reared in complex environments demonstrated superior performance in motor tasks (exploratory activity, rotorod, rotarod) and in the complex maze task. This superior performance paralleled previous observations of increased neocortical growth in environmentally enriched mice.

Effects of Fetal Neural Tissue Transplants on Behavioral Aging in Rodents. In collaboration with Drs. Talan, Bresnahan, Kametani, Kobayashi, Cutler, and Gage, we are undertaking a large study to assess the behavioral and physiological effects of fetal hypothalamic grafts placed into the third cerebral ventricles of middle-aged (16-18 mo) and aged (26 mo) male C57BL/6J mouse hosts. Our initial experiments involve testing of 30-mo old mice that have received grafts at 26-mo of age. Control groups include grafts of neocortical tissue, pieces of fat or muscle, and operated and unoperated controls. Histological examination





has verified that a high percentage (>85%) of survivors have viable grafts (large neurons, minimal gliosis, interfaced to host tissue) when the hypothalamic transplant was made to the dorsal aspect of the third ventricle. Preliminary analysis of functional tests indicate that the hypothalamic grafts may be altering the rate of age-related decline in various parameters. Promising results have been observed in core body temperature, cold tolerance, water consumption, and wheel activity tests when mice with hypothalamic grafts are compared to control groups. However, cortical grafts appear equally effective as hypothalamic grafts in affecting these parameters. Performance in other motor tests (tightrope, rotarod, rotadrum, exploratory activity) does not appear to be affected by the grafts. Other studies are now being conducted on mice with grafts in the ventral aspect of the third ventricle. The difference between the two treatments is that in the dorsal aspect of the ventricle the graft can exert only distal influence possibly through the portal or ventricular system; whereas, with the ventrally placed graft, there is the greater possibility of direct neural contact with the target hypothalamus of the host.

Methylation of DNA. The percentage of DNA 5-methyldeoxycytosine (5mdC) content in DNA is known to correlate with gene expression and different states of differentiation. Changes in the percent of 5mdC could indicate abnormal gene expression and thus an altered state of differentiation. To determine if DNA methylation changes occur during aging, the genomic 5mdC content of DNA isolated from brain, liver, and small intestine mucosa of C57BL/6J mice of 2 to 32 months of age and Peromyscus leucopus of ages 2 to 52 months of age was measured. The level of DNA 5 mdC decreased as a function of age at the rate of approximately 0.012% per month in the C57BL/6J mice but at 0.006% per month in the Peromyscus. Thus, the rate of loss of 5mdC correlates with the life span potential of these two rodent species. These results suggest that the loss of 5mdC may be an integral component of the aging process.

O<sup>6</sup>methylguanine DNA repair activity in liver as a function of increasing lifespan potential. These studies represent a collaboration with Dr. Richard Setlow of BNL and represent the first known comparative measurement of a DNA repair process in whole tissues. The preliminary results used six primate species and the two rodent species, deer mouse and field mouse. The results indicate that longer-lived species have a lower basal level of O<sup>6</sup>-methylguanine DNA repair capacity as compared to shorter-lived species.

Regulation of Physiological Functions During Aging: IV. Assessment of Primate Aging: Effects of Caloric Modification. Many interesting cross section age differences have already been observed in comparing juvenile, young adult and aged rhesus and squirrel monkeys. Most notable are a 70-80% decrease in blood alkaline phosphatase levels over the entire rhesus age span and between juvenile and adult squirrel monkeys, a 100% increase in white blood cell counts in both species, a 50% increase in rhesus blood creatinine levels, a 40% increase in rhesus immunoglobulin levels, a 50% decrease in rhesus thyroxine levels, 15-25% decreases in serum BUN's in both species and approximately 20% increases in RBC counts, hemoglobins and hematocrits in both species. In agreement with studies in other macaque colonies, blood calcium levels decline by 5-10% over the entire rhesus age span. Thus, it appears likely that some or all of the above parameters may provide sensitive aging indices with which to assess the effectiveness of the dietary modifications.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00044-14 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of Metals and Proteins on Nucleic Acid, Information Transfer and Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Gunther L. Eichhorn	Chief, LCMB	IBS LCMB NIA
Others:	James J. Butzow	Commissioned Officer	IBS LCMB NIA
	Patricia Clark	Research Chemist	IBS LCMB NIA
	Yong A. Shin	Research Chemist	IBS LCMB NIA
	Peter P. Chuknyiski (EOD 5/1/87)	Sr. Staff Fellow	IBS LCMB NIA
	Atsuko Y. Nosaka (DOD 8/21/87)	Visiting Associate	IBS LCMB NIA
	Robert E. Kilkuskie (EOD 7/1/86)	NRC Resident Research Associate	IBS LCMB NIA

## COOPERATING UNITS (if any)

See Page 2 of this Annual Report

## LAB/BRANCH

Laboratory of Cellular and Molecular Biology

## SECTION

Inorganic Biochemistry Section

## INSTITUTE AND LOCATION

National Institute on Aging/NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

7.4

## PROFESSIONAL:

6.4

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This project focuses on the interaction of molecules concerned with genetic information transfer. A primary objective is to determine under what conditions metal ions are essential for information transfer, and under what conditions they impact on the information in such a way as to influence biological aging. Topics of interest are: (1) the effects of metal ions on the structure of nucleic acids, nucleoproteins and chromatin; (2) the mechanism of involvement of aluminum in Alzheimer's disease; (3) crosslinking of nucleic acid strands by metal ions; (4) the structure of the active site of RNA polymerase; (5) metal ions and cellular aging.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00046-17 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Medicinal Chemistry Applied to Problems Prominent in Senescence

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Josef Pitha	Section Chief	MCS LCMB NIA
Others:	John Kusiak	Research Chemist	MCS LCMB NIA
	Wieslaw Buchowiecki DOD 3-31-86	Visiting Fellow	MCS LCMB NIA
	Yasuhiro Chida EOD 4-1-86	Visiting Fellow	MCS LCMB NIA
	Tetsumi Irie EOD 12-16-86	Visiting Fellow	MCS LCMB NIA

## COOPERATING UNITS (if any)

University of Florida, J. Hillis Miller Health Center, Gainesville, Florida;  
NHLBI, NIH, Bethesda, Maryland; Department of Psychology, University of  
Missouri, St. Louis, Missouri.

## LAB/BRANCH

Laboratory of Cellular and Molecular Biology

## SECTION

Macromolecular Chemistry Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland

## TOTAL MAN-YEARS:

5.25

## PROFESSIONAL:

4.25

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Alkylating prazosin, a compound which was prepared in the Section last year and which has the potential to bind permanently to adrenergic receptors of the  $\alpha_1$  type, was presently evaluated. This compound was found to bind reversibly to all receptors of this type but permanent binding was established only to a fraction of them. The results show that  $\alpha_1$ -adrenoceptors are not a homogenous group and division of these into subgroups will be necessary.

A carbostyryl derivative which fully activates and permanently binds to  $\beta$ -adrenoceptors was designed and synthesized. This compound pulls the trigger of receptors, which are in charge of the "fight or flight" reaction, and keeps the trigger pulled down for the duration. Work at the University of Florida established the correctness of the design. When  $\beta$ -adrenoceptors were activated by this compound they could not be deactivated by the addition of a  $\beta$ -blocker, a deactivation which occurred when natural, reversibly acting hormones were used for the activation.

Testosterone in the circulation of mammals rises several fold above its background levels during episodes lasting a couple of hours and occurring daily. By administration of the water soluble pharmaceutical form of testosterone, developed in the Section, these episodes may be imitated. Researchers at the University of Missouri used this preparation to establish the importance of testosterone episodes for androgen-sensitive behavior and physiology.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00047-17 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Structure-Function Relationships in Hemoglobin and Erythrocytes

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Joseph M. Rifkind	Chief, MDS	MDS LCMB NIA
Others:	Periannan Kuppusamy (EOD 3/1/86)	Visiting Fellow	MDS LCMB NIA
	Abraham Levy (EOD 8/2/87)	Sr. Staff Fellow	MDS LCMB NIA
	P.T. Manoharan (EOD 7/5/87)	Visiting Scientist	MDS LCMB NIA
	(DOD 8/4/87)		

## COOPERATING UNITS (if any)

NIA/LCS/CFS (E. Lakatta); NIA/LCP/CIS (W. Adler); IR TD/NHLBI (R. Berger);  
LMC/NCI (F. Friedman); Benedict College, Columbia, SC (K. Alston); Sandia  
National Laboratories, Albuquerque, NM (J. Shelnutz).

## LAB/BRANCH

Laboratory of Cellular and Molecular Biology

## SECTION

Molecular Dynamics Section

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00113-4 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

In Vivo NMR Studies of Aging in Cells and Animals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Gunther L. Eichhorn  
Rajasekharan P. Pillai  
EOD 7-19-87

Chief, LCMB  
Senior Staff Fellow

IBS LCMB NIA  
IBS LCMB NIA

## COOPERATING UNITS (if any)

See Page 2 of this Annual Report

## LAB/BRANCH

Laboratory of Cellular and Molecular Biology

## SECTION

Inorganic Biochemistry Section

## INSTITUTE AND LOCATION

National Institute on Aging/NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

1.3

## OTHER:

0.1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

NMR Spectroscopy is used to study the metabolic changes associated with exercise in the flexor muscle of the forearm of human volunteers. Both isometric and isotonic protocols have been developed, to be used in conjunction with a hand dynamometer. Changes in phosphocreatine (PCr) and inorganic phosphate ( $P_i$ ) as well as intracellular pH are monitored during the exercise. Age-related differences in these parameters during exercise will be studied in subjects of the BLSA.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG 00301-4 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: I. Hormone and Neurotransmitter Action.

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: G.S. Roth, Chief, Molecular Physiology and Genetic Section, LCMB, NIA  
Others:

T. Maki

J. Joseph

K. Kochman

Z. Han

B. Baum

M. Blackman

## COOPERATING UNITS (If any)

Patient Care Branch, National Institute of Dental Research; Clinical Physiology Branch, NIA Armed Forces Radiobiological Research Institute; Unit of Lab. Animal Medicine, U. of Mich.

## LAB/BRANCH

Gerontology Research Center,

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

4.5

## PROFESSIONAL:

4.0

## OTHER:

0.5

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is mainly involved in elucidating those mechanisms by which the ability of hormones and neurotransmitters to regulate physiological functions is altered during aging.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00302-4 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Physiological

Function During Aging: II. Behavioral Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Pi: Donald K. Ingram, Research Psychologist MPGS, LCMB, NIA

## Others:

C. Barnes	E. Bresnahan	R. Cutler	B. Davis
F. Gage	H. Kametani	S. Kobayashi	K. Kochman
E. D. London	T. McNeill	D. Olton	G. Roth
J. Sinnott	M. Talan		

COOPERATING UNITS (if any) Dept. Psychology, Johns Hopkins U., (D. Olton); Addiction Res. Center ADAMHA (E. London); Essex Community College, (E. Bresnahan); Lab (D. Olton); U. Colorado (C. Barnes) U. Rochester Sch. Med. (T. McNeil, B. Davis); F. Gage (U. C. San Diego, Sch. Med.)

## LAB/BRANCH

Gerontology Research Center,

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

5.8

## PROFESSIONAL:

3.5

## OTHER:

2.3

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to assess the effects of aging at a behavioral level of analysis in animal models, to identify neurobiological mechanisms associated with these effects, and to test interventions which might alter age-related performance decrements. Rodent models are tested in a battery of sensori-motor and learning/memory tasks. Neurochemical assays are conducted to determine neurobiological correlates of functional losses. Interventions include dietary restriction, environmental enrichment, various pharmacologic treatments, and neural tissue grafting. Multiple genotypes are examined to determine possible genetic involvement in the pattern of age-related behavioral impairment.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00303-4 LCMB

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Regulation of Physiological Functions During Aging: III Gene Expression and the Biology of Human Longevity

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Richard G. Cutler,	Research Chemist,	LCMB, GRC, NIA
Other:	D. K. Ingram	G. Roth	S. Ma
	I. Semsei	H. Alessio	J. Vijg
	A. Brower	J. D. Gearhart	V. Wilson
	M. Simic	M. L. Oster-Granite	R. Morgan
	A. Brown	G. Bulkley	A. H. Goldfarb
	J. Gaubatz	T. Ono	D. Bowden
	A. Brower	A. S. Kahn	D. Bergtold

COOPERATING UNITS (if any) NCI, NIH (V. Wilson); NIH, NIAID (A. Khan); NBS (M. Simic, D. Bergtold, M. Kyoto University (T. Ono); TNO (J. Vijg, A. Brower); J.K.D. Gearhart, M. L. Oster-Granite, R. Morgan, A. Brown, G. Bulkley (Johns Hopkins); Washington Reg. Primate Center (D. Bowden); UMCP (A. H. Goldfarb); U. South

LAB/BRANCH Alabama (J. Gaubatz); Brookhaven Natl. Lab. (R. Setlow); Gerontology Research Center

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.2

## PROFESSIONAL:

2.0

## OTHER:

0.2

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to gain insight into the genetic and biochemical basis determining human longevity. Our major research approach is an investigation of the molecular genetic basis of the substantial differences found in the aging rate observed in mammalian species. Research projects have centered on testing the dysdifferentiative hypothesis of aging. Here, recombinant DNA biotechnological methods are used to determine possible age-dependent alterations in gene regulation. Recent work has been centered on measuring possible age-dependent expression of endogenous retroviral genes. These include IAP genes in mice, MuLV-like genes in mice and humans and various oncogenic genes in mice and humans. Results suggest variation in expression with age that could contribute importantly to aging. Stability of the genome has been investigated by measuring total DNA 5-methylcytosine content in various tissue of Mus and Peromyscus species with age. Results have suggested a decrease



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00304-1 LCMB

PERIOD COVERED October 1, 1986 to September 30, 1987

Regulation of Physiological

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Functions During Aging: IV.  
Assessment of Primate Aging: Effects of Caloric Modification

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI's	G. S. Roth,	Chief, Molecular Physiology and Genetics Section	LCMB, NIA
	D. K. Ingram,	Research Psychologist, Molecular Physiology and Genetics Section	LCMB, NIA
	R. G. Cutler,	Research Chemist, Molecular Physiology and Genetics Section	LCMB, NIA

Others:	D. Renquist	M. April	J. Knapka
	J. Tobin	S. Sherman	M. Blackman

COOPERATING UNITS (if any)	M. Talan	W. Erschler	W. Stone
----------------------------	----------	-------------	----------

Dept. of Med. Univ. of Wisc. Madison, WI  
Dept. of Biol. Trinity Univ., San Antonio, TX

## LAB/BRANCH

Gerontology Research Center

## SECTION

Molecular Physiology and Genetics Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

2.0

## OTHER:

2.0

## CHECK APPROPRIATE BOX(ES)

- |   |  |                                      |
|---|--|--------------------------------------|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is attempting to determine whether caloric modification of the diets of rhesus and squirrel monkeys can affect aging rate as assessed by various physiological, biochemical and behavioral indices.



## ANNUAL REPORT OF THE LABORATORY OF CLINICAL PHYSIOLOGY

### NATIONAL INSTITUTE ON AGING

The Laboratory of Clinical Physiology (LCP) is comprised of four sections -- Clinical Immunology, Endocrinology, Metabolism, and Applied Physiology. The research approaches range from the more basic aspects of physiology, including molecular genetics and cell culture, to study of aging processes in experimental animals, to investigation of physiological processes in man. The human studies rely heavily on the Baltimore Longitudinal Study of Aging (BLSA) population of men and women with supplementation by special groups of individuals with characteristics which make them especially valuable for study. Thus, selected groups of middle-aged and elderly subjects who are obese or who are remarkably physically active (master's athletes) are also under study. In addition, elderly patients who are chronically hospitalized at the Francis Scott Key Medical Center (FSKMC) provide an important group of patients for studies in research geriatric medicine. While a great deal of inter-section and inter-laboratory collaboration occurs, for convenience, the activities of the Laboratory will be reported by Section.

#### Clinical Immunology Section

The clinical research in the Section is comprised of projects involving the BLSA volunteers and groups of individuals with various immunodeficiencies. The BLSA studies are directed to very basic questions in aging research. The activation of lymphocytes, the effects of cell free factors and the control of cellular function are the main points in this research. The findings show that there are several pathways for cellular activation and depending on the type and concentration of the activation signal, the cell will develop along different pathways. The connection between membrane receptor and nuclear events is of main concern. The transcription of genes for factor synthesis and membrane receptors is being studied extensively. To date the findings suggest a defect in cells from the elderly in the transcription of these genes with the resulting deficit in membrane receptor expression, factor synthesis, proliferation, and function in an immune response. The basic studies augment the clinical studies and, in particular, are directed at understanding activation events as part of the AIDS study initiatives. There is significant research activity on the study of the effects of nitrite on immune function, IL-2 receptor expression and HIV expression.

#### Endocrinology Section

Mature fat cells, isolated from perirenal or epididymal fat depots of the rat can be induced to undergo dedifferentiation in vitro. We have termed these dedifferentiating cells "postadipocytes." Postadipocytes undergo a process of breakup of their large unilocular lipid droplet. At the same time, tubular extensions of the cell membrane appear. These dendrite-like structures join with similar tubular structures arising from other cells and can be seen to transport cytoplasmic material including tiny lipid droplets. These unique cell structures may exist in vivo where they could be involved in transfer of hormonal signals between cells of the fat depot.





Another striking feature of mature fat cells in culture is the appearance of rapidly growing fibroblast-like cells. These cells originate not from the dedifferentiation of mature adipocytes but from small clusters of cells currently termed by us as "islets." These islets co-purify with mature fat cells through several flotation washes. They appear to be components of the fat depot which are closely associated with mature fat cells rather than contaminants from the stromal-vascular fraction. The clusters rapidly propagate numerous fibroblast-like cells which can overgrow the culture. The distinctness of these cells from preadipocytes is clear, since within a few days these cells undergo "spontaneous" differentiation into fat cells. Preadipocytes, in contrast, need special biochemical stimuli and undergo much less profound lipid accumulation. The existence of "islets" and their progeny cells ("islet-derived cells; IDC's") has not been previously described.

We previously reported the unique activity of rat serum in promoting cell division and biochemical maturation of preadipocytes. It was suggested that rat serum contains a large molecular weight, heat-labile growth factor for preadipocytes. The biochemical characteristics of this substance has been further defined. The factor has an apparent molecular weight of 70 kilodaltons. Heat lability is moderate. The factor is resistant to the action of proteases. The apparent species specificity of the rat serum growth factor together with its protease resistance and molecular weight strongly resemble the characteristics of colony-stimulating factor-1 (CSF-1), a highly glycosylated cell growth factor. However, the rat serum factor is distinct from CSF-1. The activity of the rat serum factor has not been simulated by a large number of known growth factors. We have termed the factor "preadipocyte-stimulating factor" or "PSF" in keeping with the name of its apparent biochemical relative, CSF-1. Additional work on the characterization of PSF is continuing. This substance may be of importance in obesity and other fat-cell related conditions.

The secretory physiology of isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perfusion in vitro culture systems. In monolayer culture, there was decreased LH and FSH release, both before and after estrogen stimulation, by pituitary cells from old vs. mature female rats. In addition, basal in vitro prolactin (PRL) secretion was increased from cells of old female rats, but decreased from cells of old male rats. However, there was an age-related decrease in PRL responsiveness to TRH stimulation and dopamine inhibition of cells from both male and female rats. There was no change with age in anterior pituitary dopamine receptor number or affinity in either sex, suggesting that "post-receptor" alteration(s) were responsible for the changes observed. In perfusion culture, coupled hypothalamic and anterior pituitary tissues from young rats exhibited rhythmic PRL secretion, apparently modulated by one or more factors from the hypothalamic fragments, providing a model for future aging studies. Molecular genetic experiments revealed increases with age in levels of stable PRL mRNA in both pituitary tissues and cells from intact female rats, both in the absence and presence of estrogen.

In the past year, our clinical studies have been oriented to (1) discriminating between the effects of primary aging vs. age-associated illness on pituitary gonadal function in men and (2) examining the interrelationships between circulating sex steroid hormone levels and various risk factors for coronary artery



disease (CAD). We have measured testosterone (T), T binding, and gonadotropins in a large group of healthy men and men with benign or malignant lung disease. We found that: (a) there is an increased prevalence of both pituitary gonadotropic and testicular dysfunction in men with lung cancer and, to a lesser extent benign lung disease and (b) the effects of illness are independent of and quantitatively greater than those of aging. We also measured plasma levels of T and estradiol (E2) in 53 men prior to their development of CAD and in 136 controls who remained without CAD. We found no significant association between levels of T, E2, or the ratio T to E2 and subsequent development of CAD. We plan to initiate or continue investigations of (a) the effects of parenteral estrogen replacement on various hormonal parameters related to bone metabolism in healthy postmenopausal women of different ages, (b) the interrelationships between sex hormones and certain CAD risk factors in healthy cycling and postmenopausal women, and (c) the effects of aging on the pituitary adrenal hormone dynamics in men and women.

### Metabolism Section

The underlying objective of the Metabolism Section (MS) is to gain an understanding of the metabolic complexities associated with aging. In the simplest terms, "primary" biological processes of aging are associated with a wide variety of "secondary" processes. The latter processes include such variables as inactivity, diet, body composition changes (lean body mass, obesity, and fat distribution pattern), and the effects of multiple disease processes and medications. On the one hand, it is our objective to dissect away the secondary effects so that true biological aging processes in man can be understood. On the other hand, the secondary processes may well prove to be of equal or greater importance in the determination of the overall picture of the aging human being. An understanding of these effects and of their relationship to primary aging processes is fundamental for the planning of rational processes to maintain health during aging and to prevent the diseases and infirmities so characteristic of the elderly.

Specifically, the research objectives of the Metabolism Section are: (1) to describe age differences and age changes in metabolic variables; (2) to determine biological mechanisms underlying those age effects; (3) to assess the impact of those age effects on other variables, on disease development, and on mortality; and (4) to define normative standards as influenced by age. The major metabolic variables include glucose homeostatic factors, insulin secretion and sensitivity to insulin, body composition including lean body mass, obesity, and fat distribution, acute effects of physical activity, long-term effects of physical fitness, and dietary variables, serum lipids, and adipose tissue metabolism.

Recent accomplishments include:

- o Further studies on the mechanisms underlying the important differences in the pattern of regional fat distribution in middle-aged and elderly men have elucidated several interesting metabolic facts. Individuals with a large waist:hip ratio have large subcutaneous abdominal adipocytes and these demonstrate three metabolic defects: increased lipoprotein lipase activity, increased alpha 2 - adrenergic inhibition of lipolysis, and decreased beta-adrenergic stimulation of lipolysis. Their gluteal fat, in contrast, shows only the single defect of reduced beta-adrenergic stimulation.



- o Characterization of the HDL subspecies has been achieved using gradient gel electrophoresis. By studying senior athletes and control subjects with widely varying fitness levels ( $VO_{2max}$ ), it was found that there is positive correlation of fitness with the HDL subspecies of 5.3 nm Stokes radius (possibly HDL 2B) and a reciprocal decrease in HDL of 4.1 nm radius (possibly HDL 3C). The former subspecies may be the moiety most highly related to the protective effects of HDL on coronary disease development.
- o Salt intake has been assessed by questionnaire (the perception of intake) and by 24-hr sodium excretion. There is little or no age difference in the perception of intake but actual intake (excretion) decreases significantly with age. There is a small but significant direct effect of salt intake on systolic blood pressure. The correlation between perceived intake and actual intake was very poor. Quantification of intake requires measurement, not history.
- o In an epidemiological search for dietary risk factors associated with colorectal polyps alcohol intake was found to be positively associated while total and complex carbohydrate and fiber intake was negatively associated with this common disorder.
- o The Baltimore Longitudinal Study of Aging population provides new standards for hematologic variables in erythrocyte variables. Aging, even into very old age, has little or no effect on these variables in women (RBC, HGB, HCT, MCV, MCHC). In contrast, in men the primary variables show a progressive decrease across the entire adult age span, but the fall in erythrocyte number is proportionately larger than that of the hematocrit; MCV thus shows a significantly large progressive increase.

#### Applied Physiology Section

The Applied Physiology Section is concerned with studying the relationship of levels, and rates of changes in levels, on performance of physiologic and non physiologic variables in health and disease. The two major areas are the long-term study of bone, both osteoporosis and osteoarthritis, and a new initiative on strength assessment. The latter effort was initiated because of the interrelationships of strength and the physical stresses of muscle on bone reabsorption and deposition. In addition, the concept of fitness has focused on aerobic conditioning ( $VO_2$  max) and its possible relationship to metabolic and cardiovascular diseases. A similar effort is necessary to define the role of muscle strength with age on some of the functional and disease changes which occur.

Other areas of interest in the section include ongoing studies on renal and glucose physiology; studies of genetic markers in an effort to understand the etiology of diseases with late onset, such as amyotrophic lateral sclerosis, parkinsonism dementia, Alzheimer's disease, osteoporosis, osteoarthritis and breast cancer; and cross cultural studies of genetic and non genetic variables in an effort to obtain a better understanding of the factors affecting normative aging processes.





Specific objectives include:

- o Characterization of the cross sectional and the longitudinal changes in cortical and trabecular bone in the spine, femoral head and neck, the ulna and radius and the metacarpal bones of the hand.
- o Elucidation of those factors which are related to bone loss including menopause, activity, strength, and nutrition.
- o Assessment of the biochemical parameters and mediators of calcium and phosphorus homeostasis and relation to those changes in bone metabolism which are ultimately reflected as changes in bone mineral content. The following parameters are studied: 1) serum calcium and serum inorganic phosphorus, 2) vitamin D status, 3) parathyroid hormone, 3) calcitonin, 4) 1,25-dihydroxyvitamin D (1,25(OH)2D3), 5) serum osteocalcin and skeletal alkaline phosphatase and 6) urinary calcium secretion.
- o Utilization of the bone mineral content information in investigating risks for osteoporosis, especially hip fractures, Colles fractures and vertebral collapse.
- o Definition of longitudinal changes in osteoarthritis of the hand and relationship to disease.
- o Utilization of dermatoglyphics, DNA minisatellites and other known genetic markers in order to understand the etiology of diseases with late onset.
- o Definition of the effects of longitudinal changes in strength in men and women on activity, nutrition, and anthropometric changes and on bone, movement, and posture.

Recent research accomplishments include the following:

- o Life table analyses of the progression of osteoarthritis of the hand in 495 males from the BLSA showed that for the more involved distal joints median time to progression to the next empirical level was independent of the starting level of pathology and ranged from 7.5 to 9.9 years. Progression in the less involved proximal joints was also independent of starting pathology and required 8.8 to >16 years to advance to the next level. These results suggest that the development and progression of radiographic osteoarthritis is time-dependent.
- o The relationship of bone loss (osteoporosis) to osteoarthritis was investigated in the 939 males of the BLSA who had hand X-rays between 1961 and 1975. Rather than the purported protective effect of arthritis against bone loss there was a positive relationship with those with the worst arthritis having significantly more bone loss. However, both bone loss and arthritis are more common in the elderly, and when adjustment was made for age there was no association. Thus, there is no protective effect of osteoarthritis of the hand on bone loss, and the apparent positive association of the two diseases was entirely explained by the effect of age.





- o Cross-sectional scans for bone density of the spine and forearm were performed on 407 male and 172 females from the BLSA. Men lost bone linearly from 20 to 90 years at a rate of .25% per year from the radius and .16% per year from the spine. Women lost bone from the radius at a rate of .21% per year from 30 to 50 years of age, accelerated to 1.3% per year from 50 to 60 years, and then slowed to .79% per year from 60 to 90. The vertebral bone loss in post menopausal women from 50 to 60 was also rapid (1.13% per year) and then slowed to .29% per year from 60 to 90.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

201-AG-00093-15-LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Basis of Regulation of the Humoral Immune Response

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: A. A. Nordin Research Chemist LCP, NIA

Others: J. J. Proust NIH Special Volunteer LCP, NIA

M. A. Buchholz Biologist LCP, NIA

F. J. Chrest Biologist LCP, NIA

## COOPERATING UNITS (if any)

C. Filburn, LBC, NIA, D. Kittur, Dept. Surgery, Johns Hopkins University,  
J. Shaper, Oncology, Johns Hopkins University, Baltimore, MD 21221.

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore Maryland 21224

## TOTAL MAN-YEARS:

3.2

## PROFESSIONAL:

2.2

## OTHER:

1

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Resting (Go) T-cells purified from the spleens of young (2-4 mo.) and old (24-27 mo.) C57BL/6 mice were used in studies to examine the effect of age on the trans-membrane signalling mechanism involving the phospholipase C induced hydrolysis of phosphatidyl-inositol 4,5 bisphosphate. Mitogenic doses of Concanavalin A (Con A) effectively induced the translocation of protein kinase C (PK-C) from cytosol to membrane in cells from young mice but in cells from old mice the level of PK-C translocated was reduced to approximate half of the level observed in the young. Total PK-C levels were the same in Go T-cells from young and old mice and phorbol 12 myristate 13 acetate (PMA) translocated equivalent levels of the enzyme irrespective of the age of the donor. Con A induced a greater change in intracellular calcium concentrations in the Go T-cells from the young mice as compared to the old both in the presence and absence of extracellular calcium. Also the detectable levels of inositol phosphates were reduced in the Con A stimulated Go T-cells from old mice. The level of these molecules, which are involved in regulating intracellular calcium concentration, were also reduced by approximately 50% of that detected in cells from young mice. PK-C levels and the capacity to translocate from cytosol to membrane were the same in T lymphocytes from young (less than 35 yrs) and old (greater than 70 yrs) human males in response to PMA. In response to PHA, T-cells from some but not all old subjects translocated low levels of PK-C. Studies are planned to extend the investigations using human T-cells to determine intracellular calcium levels and to correlate deficiencies in the transmembrane signalling mechanism with expression of functional IL-2 receptors and/or IL-2 production.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00095-14-LCP

## PERIOD COVERED

October 1, 1986 - September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

The Role of Cell Membrane Structures on Cellular Recognition

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer, PHS	LCP, NIA
Others:	J. E. Nagel	Medical Officer, PHS	LCP, NIA
	R. K. Chopra	Visiting Fellow	LCP, NIA
	W. O. Boto	NRC Fellow	LCP, NIA
	S. D. Kittur	Medical Staff Fellow	LCP, NIA EOD 4/87
	J. J. K. Hoh	Medical Staff Fellow	LCP, NIA EOD 7/87
	D. C. Powers	Medical Staff Fellow	LCP, NIA EOD 7/87

## COOPERATING UNITS (if any)

Drs. R. Winchurch, D. Kittur and S. Xu - Dept. of Surgery, Dr. M. Liu, Dept. of Medicine, FSK Medical Center, Johns Hopkins Univ., Drs. E. Dax and R. Lange, NIDA, Balto., MD 21224, Dr. A. Piirsoo - IREX Fellow, left 3/87.

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

5.6

## PROFESSIONAL:

2.9

## OTHER:

2.7

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☒ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Activation of lymphocytes proceeds through a complicated series of events. The events can be influenced by drugs, cell free products, and products of an inflammatory response. Amyl nitrite use causes lymphopenia and subsequent lymphocyte stimulation. Activated cells express new proteins and shed IL-2 receptors from the membrane. The IL-2R shed relates to the degree of activation and can bind IL-2. Its suppressive effects on IL-2 driven reactions is variable due to its binding to IL-2 prior to its use as a suppressive factor. There are suppressive factors which disrupt NK activity on YAC target cells. Trace metals such as zinc can modulate IL-1 and IL-2 activity and augment antibody formation. IL-2 can cause gene rearrangement for immunoglobulin synthesis by human B cells. Activation pathways, membrane events, nuclear events and factor elaboration are all important events and have all been implicated in some forms of immuno-deficiency.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00096-14-LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Lymphocyte Activation and Function in Aging Individuals

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	M. A. Brock	Research Biologist	LCP, NIA
Others:	W. H. Adler	Medical Officer, PHS	LCP, NIA
	R. S. Pyle	Bio. Lab. Tech.	LCP, NIA

## COOPERATING UNITS (if any)

H. J. Hoffman, D. W. Denman III, Biometry Branch, NICHD

## LAB/BRANCH

Gerontology Research Center, Laboratory Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.3

## PROFESSIONAL:

1.2

## OTHER:

.1

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Previous Title: Low Temperature Effects on Cells of Aging Individuals

The effects of agents which can perturb the cytoskeleton were studied in T lymphocytes from aging mice. Single cell suspensions of splenocytes and resting T cells were prepared from the spleens of young and senescent C57BL/6 mice. These populations of cells either were stimulated with the T cell mitogen, Concanavalin A, cytochalasin B and E, ionomycin, IL2 or various combinations of those or they were attached to cover slips for analysis of single cells. Levels of mitogenesis of the stimulated cells were assessed by tritiated thymidine incorporation.

No age-related differences were observed in the activation of splenocytes and resting T cells by cytochalasin B. The highest levels of proliferation induced by Concanavalin A were unaffected by adding optimal concentrations of cytochalasin B, however, at nonoptimal Concanavalin A concentrations, cytochalasin B synergized resulting in 2-3 fold increases in proliferation of splenocytes and resting T cells from both young and old mice. Tritiated thymidine incorporation reached 40-60% of the maximal induced by Concanavalin A alone. These results suggest that cytochalasin B sensitive elements of the cytoskeleton such as actin are involved in T cell activation with no decrease in sensitivity in lymphocytes from older mice.

The significance of this project is in understanding the possible role of cytoskeletal components and growth factors in lymphocyte signal transduction and whether the observed decline in immune function with age can be attributed to alterations in cytoskeletal organization.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01-AG-00104-11-LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Clinical Immune Survey of the Longitudinal Project Participants\*

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	W. H. Adler	Medical Officer	LCP, NIA
Others:	*J. J. Proust	Visiting Associate	LCP, NIA
	J. E. Nagel	Medical Officer	LCP, NIA
	R. K. Chopra	Visiting Fellow	LCP, NIA
	F. J. Chrest	Biologist	LCP, NIA
	R. S. Pyle	Bio. Lab Tech.	LCP, NIA
	J. J. K. Hoh	Medical Staff Fellow	LCP, NIA EOD 7/87
	D. C. Powers	Medical Staff Fellow	LCP, NIA EOD 7/87

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Clinical Immunology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

3.4

## PROFESSIONAL:

2.7

## OTHER:

.7

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

These studies collect information on the immune function of participants in the Baltimore Longitudinal Study of Aging to determine age-associated changes, and to determine the relationship of these changes to an individuals diet, exercise habits, psychological coping mechanisms as well as to the development of clinical diseases. A further ongoing goal is to evaluate existing assays of immune function in regards to their ability to provide an accurate and clinically useful assessment of human immune competence.

Others:	*B. A. Dorsey	Bio. Lab Tech.	LCP, NIA
	W. M. Boto	NRC Fellow	LCP, NIA EOD 3/86



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00011-14 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging. I. Adenylate Cyclase and Hormone Action

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

R.I. Gregerman, M.D., Chief, Endocrinology Section, Laboratory of Clinical  
(Unit I) Physiology, National Institute on Aging

## COOPERATING UNITS (if any)

Department of Medicine, Francis Scott Key Medical Center  
Endocrinology Division, University of Texas Health Sciences  
Center, San Antonio

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Endocrinology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☒ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

This project initiates studies of age-related alterations of hormone action. Recent focus has been on the actions of hormones which act through components of cell membranes, especially those of the hormone-sensitive adenylate cyclase complex. These components include hormone receptors and regulatory proteins. Aging in fat cells is being studied in tissue culture of preadipocytes and dedifferentiated mature fat cells (postadipocytes) from rats.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00013-12 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones, Hormone Receptors, and Aging. III. Aging and Human Endocrine Regulation

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, LCP, NIA

Other: Marc R. Blackman, M.D. Guest Scientist LCP, NIA

Carlo Contoreggi, M.D. Medical Staff Fellow LCP, NIA

## COOPERATING UNITS (if any)

Dept. of Medicine, F.S.K. Med. Center and J.H.U. Medical School  
Metabolism Section, LCP and LCS, GRC

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Endocrinology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.2

## PROFESSIONAL:

1.0

## OTHER:

.2

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In the past year, our clinical studies have been oriented to (1) discriminating between the effects of primary aging vs. age-associated illness on pituitary gonadal function in men and (2) examining the interrelationships between circulating sex steroid hormone levels and various risk factors for coronary artery disease (CAD). We have measured testosterone (T), T binding, and gonadotropins in a large group of healthy men and men with benign or malignant lung disease. We found that: (a) there is an increased prevalence of both pituitary gonadotropic and testicular dysfunction in men with lung cancer and, to a lesser extent benign lung disease and (b) the effects of illness are independent of and quantitatively greater than those of aging. We also measured plasma levels of T and estradiol (E2) in 53 men prior to their development of CAD and in 136 controls who remained without CAD. We found no significant association between levels of T, E2, or the ratio T to E2 and subsequent development of CAD. We plan to initiate or continue investigations of (a) the effects of parenteral estrogen replacement on various hormonal parameters related to bone metabolism in healthy postmenopausal women of different ages, (b) the interrelationships between sex hormones and certain CAD risk factors in healthy cycling and postmenopausal women, and (c) the effects of aging on the pituitary adrenal hormone dynamics in men and women.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00023-11 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Hormones and Aging II-Pituitary and Hypothalamic Function in Experimental Animals

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

S. M. Harman, M.D., Senior Investigator, LCB, NIA

## Other:

M. R. Blackman, M.D. Guest Scientist LCP, NIA  
Carlo S. Contoreggi, M.D. Medical Staff Fellow LCP, NIA  
George S. Roth, Ph.D. Section Chief MPGS, LCMB, NIA  
K. Kochman, Ph.D. Visiting Scientist MPGS, LCMB, NIA  
David Danner, M.D., Ph.D. Section Chief IMG, NIA

## COOPERATING UNITS (if any)

Molecular Physiology and Genetics Section, LCMB, GRC  
Laboratory of Molecular Genetics, GRC  
Dept. of Medicine, F.S.K. Med. Center and J.H.U. Medical School

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Endocrinology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.2

## PROFESSIONAL:

1.6

## OTHER:

.6

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The secretory physiology of isolated cells and tissues from anterior pituitary glands of old vs. mature male and female rats has been studied in both static monolayer and dynamic perfusion in vitro culture systems. In monolayer culture, there was decreased LH and FSH release, both before and after estrogen stimulation, by pituitary cells from old vs. mature female rats. In addition, basal in vitro prolactin (PRL) secretion was increased from cells of old female rats, but decreased from cells of old male rats. However, there was an age-related decrease in PRL responsivity to TRH stimulation and dopamine inhibition of cells from both male and female rats. There was no change with age in anterior pituitary dopamine receptor number or affinity in either sex, suggesting that "post-receptor" alteration(s) were responsible for the changes observed. In perfusion culture, coupled hypothalamic and anterior pituitary tissues from young rats exhibited rhythmic PRL secretion, apparently modulated by one or more factors from the hypothalamic fragments, providing a model for future aging studies. Molecular genetic experiments revealed increases with age in levels of stable PRL mRNA in both pituitary tissues and cells from intact female rats, both in the absence and presence of estrogen.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 00204-4 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic Studies in the Baltimore Longitudinal Study of Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Reubin Andres, M.D.

Chief, Metabolism Section, LCP, NIA

Jordan Tobin, M.D.

Chief, Human Performance Section, LCP, NIA

Judith Hallfrisch, Ph.D.

Senior Staff Fellow, LCP, NIA

Hiroshi Shimokata, M.D.

Visiting Fellow, LCP, NIA

Donald Drinkwater, Ph.D.

Visiting Fellow, LCP, NIA

Denis Muller, B.S.

Chemist, LCP, NIA

## COOPERATING UNITS (if any)

Division of Geriatric Medicine, Department of Medicine, Francis Scott Key Medical Center, Johns Hopkins University, Janette Busby, M.D., Assistant Professor and Patricia Coon, M.D., Assistant Professor

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Metabolism Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

2.80

## PROFESSIONAL:

1.05

## OTHER:

1.75

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Aging is characterized by a host of changes in metabolic variables which have profound effects on disease development and on survival. The BLSA provides the opportunity to conduct analyses on these variables to relate them to other characteristics of the individual, and to analyze for long-term effects of these complex interactions. Variables which are potentially alterable by changes in life style characteristics (diet, body weight, activity level) are of especial importance in this respect. Age-specific normative data are required and can only be determined rationally by analyses such as these. Dietary diary information has been obtained on 445 men and women. This will provide an important update on secular changes in the diet since the 1961-1975 dietary information was obtained. Salt intake has been assessed by questionnaire (the perception of intake) and by 24-hr sodium excretion. There is little or no age difference in the perception of intake but actual intake (excretion) decreases significantly with age. There is a small but significant direct effect of salt intake on systolic blood pressure. The correlation between perceived intake and actual intake was very poor. Quantification of intake requires measurement, not history. Rectal and colonic polyps were associated with several dietary variables: alcohol (positive effect) and carbohydrate and fiber intake (negative effect).



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00205-4 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Body Fat Distribution Pattern in the Baltimore Longitudinal Study of Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Hiroshi Shimokata, M.D. Visiting Fellow, Metabolism Section, LCP, NIA  
Denis Muller, B.S. Chemist, Metabolism Section, LCP, NIA  
Reubin Andres, M.D. Chief, Metabolism Section, LCP, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Metabolism Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.70

## PROFESSIONAL:

1.15

## OTHER:

0.55

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A remarkable variety of clinical variables have been shown to be related to the body fat distribution. Many studies have shown that the waist hip ratio (WHR) is not only a simple index of the fat distribution pattern, but is also a powerful predictor of risk factors, diseases, and mortality. Despite extensive literature, systematic information on the distribution of values for the two components of the WHR (waist and hip circumference), for the ratio itself, and for changes in these values with change of weight is not available. The effects of age, sex and change in weight on WHR were examined in the BLSA subjects. Cross-sectionally, in men there was small increase in waist and small decrease in hip with increasing age, so that WHR increased by 0.001 per year of age. Although both waist and hip increased with age in women, the increase in waist was much larger than hip, so that the WHR increased by 0.002 per year of age. Longitudinally, weight change correlated positively with change of waist and hip in both sexes. In men change in waist was much larger than change in hip. In women change in hip was slightly larger than change in waist. On the average, these circumferential changes with weight result in large changes in WHR in men; in women the changes are rather proportional to the original ratio and only very small, generally insignificant, changes in the WHR occur.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00208-3 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging, Obesity, Sedentariness and Endocrine-Metabolic Function

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Donald Drinkwater, Ph.D. Visiting Fellow, LCP, NIA  
Roy Verdery, Ph.D., M.D. Medical Staff Fellow, LCP, NIA  
Reubin Andres, M.D. Chief, Metabolism Section, LCP, GRC, NIA

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center, The Johns Hopkins Hospital

Andrew Goldberg, M.D. Eugene Bleecker, M.D. Loretta Lakatta, R.N.

Ellen Rogus, Ph.D. Adriane Kozlovsky, R.D.

Patricia Coon, M.D. Marilyn Lumpkin, M.A.

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Metabolism Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.95

## PROFESSIONAL:

0.80

## OTHER:

1.15

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Obesity, sedentariness and aging are associated with hyperlipidemia, glucose intolerance, and altered sympathoadrenal responsiveness. To determine the relationships among these variables, this study examines glucose and lipid metabolism and sympatho-adrenal function in obese, sedentary men aged 45-75 years at entry into the study and again after either weight reduction or aerobic training. The endocrine-metabolic functions being evaluated are: 1) insulin secretion and sensitivity assessed by euglycemic and hyperglycemic clamps; 2) lipoprotein metabolism by lipoprotein lipid profiles, high density lipoprotein (HDL) subspecies levels and lipoprotein lipase activity in postheparin plasma and adipose tissue; 3) the regulation of adipose tissue metabolism and fat cell size by fitness ( $\dot{V}O_{2max}$ ), fatness (% body fat) and the regional distribution of body fat (waist:hip circumferential ratio) by studying the responsiveness of adipose tissue from upper and lower body sites to beta-and alpha<sub>2</sub>-adrenergic stimuli; and 4) sympathoadrenal responses to upright posture, oral glucose, and hyperinsulinemia during a euglycemic clamp. A total of 132 subjects have completed baseline metabolic studies and have been randomized to either the weight reduction or aerobic exercise training interventions. At baseline these men have low levels of physical fitness, impaired glucose tolerance, increased insulin resistance, and low plasma levels of HDL cholesterol (HDL-C) when compared to age-matched, lean controls. Twenty subjects have completed the weight loss program and 14 the exercise program. With weight loss there was a significant improvement in a number of metabolic parameters with no change in their maximal aerobic capacity. In 9 subjects whose  $\dot{V}O_{2max}$  increased >15%, insulin sensitivity and HDL-C rose, triglyceride decreased and fat cell size got smaller, presumably due to an increase in stimulated lipolysis secondary to increased sensitivity to beta-adrenergic agonists. There are currently 25 subjects in the weight loss group, 20 in the exercise group, and 12 subjects are in various phases of baseline testing prior to randomization.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00209-3 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging and Cardiovascular, Endocrine and Metabolic Function in Master Athletes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Donald Drinkwater, Ph.D. Visiting Fellow, LCP, NIA  
 Roy Verdery, Ph.D., M.D. Medical Staff Fellow, LCP, NIA  
 Janette Busby, M.D. Medical Staff Fellow, LCP, NIA  
 Reubin Andres, M.D. Chief, Metabolism Section, LCP, NIA  
 Edward Lakatta, M.D. Chief, LCS, NIA  
 Jerome Fleg, M.D. Scientist, LCS, NIA  
 Judith Hallfrisch, Ph.D. Senior Staff Fellow, LCP, NIA  
 Chris Plato, Ph.D./Jordan Tobin, M.D., Applied Physiology Section, LCP, NIA

COOPERATING UNITS (if any)

Francis Scott Mey Medical Center, Johns Hopkins University  
 Department of Medicine, Johns Hopkins University  
 The Johns Hopkins School of Hygiene and Public Health

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Metabolism Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

2.151.001.15

CHECK APPROPRIATE BOXES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Endurance exercise training elicits physiological adaptations which increase the functional capacity of various organs. Older, physically well-trained "master" athletes tend to have a cardiovascular functional capacity (maximal oxygen consumption,  $VO_{2max}$ ) which more closely approximates that of much younger individuals than that of their sedentary peers. They also have higher levels of high density lipoprotein (HDL) cholesterol, lower percent body fat and their tissues are more insulin sensitive than that of age-matched sedentary controls. The interrelationship of age and physical fitness to endocrine-metabolic function, (lipid profiles, lipid metabolism, glucose metabolic rates and insulin sensitivity), and cardiovascular function is being examined in healthy lean older men (>60 yrs), free of detectable coronary artery disease and metabolic dysfunction, and who have a wide range (25-50+ ml/kg.min) of  $VO_{2max}$ . The specific role of training on metabolic and cardiovascular function will be determined by deconditioning highly trained individuals over a 3 mo period and conditioning sedentary and less active subjects over a 6-9 month period, such that both groups achieve a common level of  $VO_{2max}$ . Endocrine-metabolic function studies include: 1) glucose tolerance, beta cell sensitivity, and insulin sensitivity, 2) lipoprotein metabolism and lipoprotein lipase activity, and 3) sympathoadrenal responses to cycle exercise, and to lower body negative pressure. Baseline fasting glucose and lipid profiles have been obtained on 83 participants. Seventy-eight subjects have had oral glucose tolerance tests, and 68 of the men qualified have undergone an initial treadmill screening test and maximal oxygen consumption ( $VO_{2max}$ ) test, 59 have undergone a second  $VO_{2max}$  test and thallium scans, 8 have undergone hyperglycemic clamps with measurements of insulin receptor binding, 13 have undergone multigated cardiac blood pool scans and 13 have had HDL subfraction analysis with measurement of postheparin plasma lipoprotein lipase activity.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00210-2 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Decubitus Ulcers and Cachexia: Diet and Cell Biology

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Roy Verdery, M.D.

Medical Staff Fellow, LCP, NIA

Judith Hallfrisch, Ph.D.

Senior Staff Fellow, LCP, NIA

Rosalind Breslow, M.S.

Guest Investigator (Ph.D. Candidate), LCP, NIA

## COOPERATING UNITS (if any)

Andrew P. Goldberg, M.D., Director, GCRC

Francis Scott Key Medical Center, Johns Hopkins University

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Metabolism Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

1.40

## PROFESSIONAL:

1.00

## OTHER:

0.40

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

There are two aspects to this study. One is a clinical dietary intervention study on the healing of decubiti. The second is a study of biological variables underlying the development of decubiti and cachexia. The project is designed to test the hypothesis that patients with cachexia, characterized by low lean body mass, anemia, hypoalbuminemia and/or hypocholesterolemia have impaired cell growth and metabolism because of low levels of circulating lipoproteins, low levels of a cellular growth factor, or elevated levels of an inhibitory factor. In vitro systems using fibroblast cell proliferation, measured by <sup>3</sup>H-thymidine incorporation into DNA, is being used to assay plasma and sera from elderly subjects for growth-stimulatory or inhibitory substances. This project may give insight into the mechanisms causing weight loss and promoting the occurrence of decubitus skin ulcers in the elderly.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00021-24 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Study of Normal Human Variability and Cross Cultural Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.C. Plato

Sr. Research Geneticist

LCP NIA

## COOPERATING UNITS (if any)

See attached page.

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Applied Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS:

0.40

## PROFESSIONAL:

0.20

## OTHER:

0.20

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project represents an ongoing collaborative effort, involving WHO and other national and international laboratories to coordinate the collection, evaluation and interpretation of normal genetic markers, in order to, study the cross-cultural patterns of genetic and extraneous factors as they relate to normative aging and to diseases with late onset. Specifically, the objectives of this study are: A) To study the distribution of DNA minisatellites, dermatoglyphics, lateral dominance and other genetic variables in BLSA participants and other control samples, as well as in patients with late onset diseases. B) To study the genetic segregation of these markers in families with late onset diseases, such as Alzheimer's disease, breast cancer, ALS and others, in an effort to establish genetic linkages and eventual identification of the factors responsible for these diseases and C) To study the cross cultural patterns of genetic and non genetic factors in an effort to better understand the process of normative aging.





DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00022-11 LCP

PERIOD COVERED October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Investigations of Bone Mineral Density and Bone Loss

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.C. Plato

Sr. Research Geneticist

LCP NIA

COOPERATING UNITS (if any)

Laboratory of Central Nervous System Studies, NINCDS

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

4.0

PROFESSIONAL:

1.5

OTHER:

2.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects

☐ (b) Human tissues

☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Bone loss together with osteoarthritis (see project Z01 AG 00290-02 LCP entitled "Osteoarthritis and Aging") is one of the two principal age related changes of the human skeleton. Even though these changes are considered universal phenomena inherent to aging, they may result in incapacitating ailments. Advanced bone loss may result in osteoporosis and frequent bone fractures. At some time during the fourth decade of life, the human skeleton begins to lose bone. That is, bone mass decreases in relation to bone volume. In tabular bones, bone is resorbed from the endosteal surface. Because of the thinning of the cortical bone shell, bones lose their mechanical integrity and fracture more readily. The trabecular bone mass of the vertebral column also decreases with age. The vertebral plates decrease in density, lose resistance to vertical compression stress and are more vulnerable to vertebral collapse. Vertebral compression fractures and fractures of the femoral neck are the most serious consequences of bone loss. The following skeletal sites are involved in the present study: hand-wrist, ulna and radius, vertebral column and the proximal femur (trochanter, neck and Wards triangle). This project deals with the epidemiological, genetic, longitudinal and biochemical aspects of bone loss (1) among the participants of the Baltimore Longitudinal Study, (2) in a sample of normal adult Guamanians (Chamorro), (3) among patients afflicted with Amyotrophic Lateral Sclerosis/Parkinsonism Dementia Complex of Guam, (4) to ascertain bone mineral differences between long distance runners and relatively inactive normal controls, and (5) study of bone mineral density and effect of muscular activity on bone in rats and other animals.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00028-11 LCP

PERIOD COVERED October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Epidemiological &amp; Genetic Studies of ALS/PD Complex of Guam

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

C.C. Plato

Sr. Research Geneticist

LCP NIA

COOPERATING UNITS (if any)

C &amp; F Research, NINCDS

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

0.15

PROFESSIONAL:

0.10

OTHER:

0.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In an effort to elucidate the etiology of high incidence of Amyotrophic Lateral Sclerosis (ALS) and Parkinsonism Dementia (PD) on the island of Guam, a patient-control prospective study (Registry) was established in 1958. The Registry includes, in addition to the patients and their individually matched controls, their respective parents, sibs, offspring and spouses. The objective of the registry has been to determine (1) whether relatives of ALS and PD patients have higher risk for developing the disease than relatives of controls and (2) if familial occurrence does exist, to determine the extent of genetic involvement in the etiology of the disease. A twenty-five year follow-up analysis of the registry has just been concluded and the results are published.

Other objectives of this study are: 1) to investigate the genetic and epidemiological factors contributing to the very high incidence of Amyotrophic Lateral Sclerosis and Parkinsonism Dementia (ALS/PD) on Guam; 2) to evaluate the distribution of the various established genetic and anthropological markers among the normal Guamanian population and compare them with those of the ALS/PD patients; and 3) to ascertain the effects of immobilization due to paralysis on bone density.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00290-02 LCP

PERIOD COVERED October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Osteoarthritis and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

M.J. Busby

Medical Staff Fellow

LCP NIA

COOPERATING UNITS (if any)

Rheumatology, Francis Scott Key Medical Ctr.  
Laboratory of Personality & Cognition, NIA

LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

SECTION

Applied Physiology Section

INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS:

1.2

PROFESSIONAL:

0.8

OTHER:

0.4

CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

The most common rheumatic disease of the elderly is osteoarthritis. Forty million Americans are estimated to have radiological evidence of osteoarthritis; the majority are asymptomatic. Progressive increases in both numbers of persons involved and extent of osteoarthritic changes are known to occur with aging. However, it is not clear whether the rate of progression is the same in young, middleaged, and older persons. Similarly, the rate of development of osteoarthritis is not well defined. A controversy also exists regarding exactly where on the established scale of measurement for radiographic changes (0 to 4+, with 2+ considered to be definite disease) osteoarthritis actually begins. Cross-sectional studies provide valuable prevalence or correlative data and are important in determining the relationship between radiographic disease, symptoms, treatment, and functional status. Longitudinal studies provide the insight into the natural history and long progression of aging and disease states.

This project is both a longitudinal study designed to determine the progression of osteoarthritis by evaluation of radiographic changes on hand X-rays and a correlative study to examine the interrelationship of symptoms, physical exams, and X-rays in several joints.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00291-02 LCP

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Physiology of Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Jordan D. Tobin

Chief, Applied Physiology Section LCP NIA

## COOPERATING UNITS (if any)

Metabolism Section, NIA, NIH

VA Med. Ctr. Wash., DC

Cognition Section, NIA, NIH

Francis Scott Key Medical Center

## LAB/BRANCH

Gerontology Research Center, Laboratory of Clinical Physiology

## SECTION

Applied Physiology Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Maryland 21224

## TOTAL MAN-YEARS

0.65

## PROFESSIONAL:

0.4

## OTHER:

0.25

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Studies of age changes in physiologic systems have included renal, cardiovascular, and metabolic areas. Of particular interest, has been the relationship of dietary intake of nutrients to physiology. These have included the effects of protein intake on renal function (creatinine clearance), the effect of calcium and protein intake on bone loss, and the effect of dietary fiber intake on cardiovascular risk factors.

The effects of both protein intake and calcium intake differed from those theorized. Thus, higher protein intake had no effect on simultaneous renal function nor did it have any effect on kidney function measured at least 10 years after diet estimates. Similarly calcium intake (considered with and without protein estimates) had no relationship to bone mineral (estimated on X-ray by the thickness of cortical bone) either at the same time as the dietary measurements or at least 10 years later. Fiber estimates were related to certain risk factors for cardiac disease (blood pressure, triglyceride and fasting plasma glucose) (see Metabolism Section).

The two hour glucose levels of females undergoing glucose tolerance tests was not related to psychological tests of memory, vocabulary, or reaction time but were significantly related to performance on a test of cognitive ability (conceptual problem solving).

Mean blood pressure values were not related to the rate of fall in renal function in 254 normal men with blood pressures in the normal range. When higher levels of blood pressure were included in the analysis there was a relationship with higher pressures being associated with more rapid loss of renal function.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00292-01 LCP

PERIOD COVERED October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
BLSA Physical Activity Questionnaire Study

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Linda P. Fried Visiting Scientist LCP NIA

## COOPERATING UNITS (if any)

Laboratory of Cardiovascular Science, NIA, NIH  
Longitudinal Studies Branch, NIA, NIH

LAB/BRANCH Gerontology Research Center, Laboratory of Clinical Physiology

SECTION Applied Physiology Section

INSTITUTE AND LOCATION NIA, NIH, Baltimore, Maryland 21224

TOTAL MAN-YEARS: 1.1 PROFESSIONAL: 0.6 OTHER: 0.5

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is designed to determine the reliability and validity of questionnaire components in relation to physiologic measures of physical activity and fitness. This study consists of (1) a retrospective analysis of physical activity data collected biannually in the BLSA to describe change in physical activity levels over time and variation by age and sex, and the questions most strongly associated with treadmill-assessed fitness; (2) a prospectively-administered questionnaire to assess reliability of retrospective recall of physical activity as compared with previous self-report; and (3) prospective discrimination of the relationships between treadmill-measured fitness and daily activity (as measured by activity monitor and activity diary) with questionnaire assessment of habitual physical activity. This study will result in development of a questionnaire to assess physical activity levels in the BLSA population that has optimal validity for adults of all ages, and for both men and women. Development of such an instrument will maximize the validity of studies on the relationship between habitual physical activity levels and aging, health, and disease.



National Institute on Aging

The overall objective of this laboratory is to apply recently advanced techniques of molecular genetics to the study of the aging process and age-related diseases. Attempts to clone genes differentially expressed with aging are being pursued with whole mouse and rat brain tissues. A search is being conducted for genes that inhibit cell growth in cultured human fibroblasts. Age-dependent changes in the immune and endocrine systems are being studied at the molecular level to determine if gene expression is altered with aging. Other projects being conducted include examination of age-dependent changes in DNA repair and neoplastic transformation, and identification of possible enzymatic activity or DNA fingerprinting patterns linked to age-related disorders such as Alzheimer's and Huntington's diseases.

Molecular basis for decreased immune function in aging humans and rats

It is well established from human and animal studies that there is a general decrease in immune function that occurs with aging. This project focuses on examining the cause(s) for this decline at the molecular level. In particular, we have focused on the activation of T lymphocytes by mitogen. Three T-cell proteins have been examined thus far: interleukin 2 (IL-2), a lymphokine absolutely required for the proliferation of certain T cell populations; IL-2 receptor (IL-2R), the cell surface receptor for IL-2; and interferon gamma, another lymphokine whose regulation is intimately linked to IL-2. Expression of the IL-2 and IL-2R genes in human peripheral blood lymphocytes (PBL) was examined from 13 young and 17 elderly donors. In addition to decreased proliferative capacity, elderly individuals displayed a significant decrease in the amount of IL-2 protein activity and expression of IL-2R relative to younger individuals. These decreases were accompanied by decreased levels of IL-2 and IL-2R specific mRNA. Similar results have been obtained with interferon gamma in a smaller number of donors. Thus, it appears that decreased induction of all three of these genes upon antigenic stimulation contributes to diminished T cell functions observed in the elderly.

Isolation of genes differentially expressed in the brains of old and young rats

Despite the structural, and biochemical changes reported to occur in aging brain, the mechanism(s) underlying the aging process itself remain unknown. Thus, we have begun a new project designed to explore differential gene expression in old and young rat brain. Using subtraction hybridization techniques we are attempting to clone genes which are differentially expressed in aged (24 month) and mature young (5 month) rats. Briefly, the





basic approach is to construct two cDNA libraries; one from poly A+ RNA from young rats, the other from poly A+ RNA from old rats. Poly A+ RNA from one age group is hybridized to the cDNA derived from the opposite age group and the cDNA/mRNA hybrids removed. As a result, nonhybridizing cDNAs obtained and subsequently packaged in a bacterial vector, should be enriched or highly specific for a particular age group. Ultimately, this will give us the opportunity to identify and study those genes which are involved (associated) with the aging process in brain by virtue of their increased expression (or conversely, by their relative inactivity) at specific ages.

#### Regulation of interleukin 2 gene expression in lymphoid and nonlymphoid cells

This project is focused at understanding the basic control mechanisms responsible for expression of the human interleukin 2 (IL-2) gene. Particular items addressed are as follows: 1) Expression of the human IL-2 gene in various cell types - Ordinarily, human IL-2 is expressed only in T cells where it is under tight inducible control. We have stably transfected the human IL-2 gene into mouse fibroblasts and a human epithelial cell line. In both cases the gene is constitutively expressed. The expressed mRNA is not of the expected size, however. RNA mapping experiments have been used to define the basis for its altered expression. 2) The mechanism for activation of IL-2 expression in MLA 144 cells by a retroviral insertion - The role of the viral regulatory elements in influencing IL-2 expression in transient systems has been investigated. 3) The role of 3' sequences in controlling IL-2 expression has been examined.

#### Transcriptional control elements in the gibbon ape leukemia virus LTR

Studies were undertaken to localize precisely the transcriptional enhancer elements within the long terminal repeats (LTRs) of different gibbon ape leukemia virus (GALV) strains and identify the cellular factor which binds to the enhancer region.

1) We have shown that the major element responsible for enhancer activity of the GALV LTR is contained within a 12 bp sequence of a 45 bp repeated DNA segment.

2) Using exonuclease III and DNase I footprinting techniques we have identified a nuclear factor which binds specifically to the 12 bp enhancer sequence. It is present in cells which express GALV to high levels but not in cells which express GALV poorly.

3) We have demonstrated that the tumor promoter phorbol myristate acetate can enhance transcriptional activity of the GALV LTR 50-100 fold in various lymphoid cell lines. It also enhances expression of several other viral transcriptional elements including SV40, human T cell lymphotropic virus type I,





and Rous sarcoma virus, suggesting it works via a generalized mechanism. For practical purposes, PMA provides a convenient means for increasing transient expression of foreign DNA in lymphoid cells.

#### Molecular genetic analysis of Alzheimer's disease

Dr. John Blass at Cornell has shown that the activity of three thiamine-dependent enzymes--transketolase, alphaketoglutarate dehydrogenase, and pyruvate dehydrogenase--are decreased in two dementias, Wernicke-Korsakoff Syndrome and Alzheimer's disease. In general, this decrease occurs in body tissues not directly affected by the disease process; this suggests that inactivation of these enzymes is not simply an effect of the underlying pathology but may be intimately related to the cause of each disease, perhaps directly or perhaps as a predisposing factor. The goal of this project is to clone the genes for these enzymes, beginning with transketolase, by screening cDNA expression libraries from human brain and liver with antibodies made by the Blass group and with synthetic oligonucleotides whose sequence will be derived from microsequencing of purified protein provided by the Blass group. The cloned DNAs for these genes will then be used as probes to analyze the structure and function of the genes in Alzheimer and Wernicke patients versus normal controls.

We have also completed a small pilot experiment to analyze Alzheimer brain for reverse transcriptase, in order to ask if a retrovirus might play a role in this disease.

#### Analysis of changes in hormone expression with age

Harman and Blackman, LCP, NIA have shown that basal and stimulated levels of luteinizing hormone decline with age in the rat pituitary, and Roth, LCMB, NIA has shown that basal and stimulated levels of prolactin increase in the same system. We will be asking the question whether these age-related hormone changes are reflected in the level of messenger RNA produced by the hormone genes. This will be done by quantitative hybridization analysis of pituitary messenger RNA using cloned hormone gene probes. If message levels are altered, we will proceed to ask whether the changes are at the level of the gene or in the regulatory pathway controlling the gene. This will be done by assaying the expression of a control exogenous hormone gene in the environment of the old and young cell. This analysis should ultimately allow us to pinpoint the defect that aging produces in this regulatory circuit, and may have implications for the effect of aging on other regulated genes.

#### Cloning of a gene involved in shutting off cell growth

Smith has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into the same cell type at early passage, the growth of the early passage cells is



halted. A functionally identical activity derived from rat liver (by K. McClung and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We plan to clone this mRNA by hybrid selection screening of a cDNA library, and then to analyze the structure and expression of the gene.

#### Identification of age-related transcripts in the mouse

We are searching for messenger RNA's that are differentially produced during the lifespan of mice. Our approach to this analysis is to make cDNA libraries from young (3 month) and old (27 month) mice from the GRC colony. These libraries will be compared by hybridization techniques to see what RNA messages are present in high copy in one library but not in another. The structure and tissue-specific expression of these messages will then be examined.

#### Analysis of allelic exclusion in transgenic mice

Allelic exclusion is the process by which antibody-producing cells (B cells) shut down or exclude from expression one of their two antibody genes after they have started expressing the first. This selectivity is critical to an effective immune response, since it allows each clone of B cells to respond to one particular antigen. The mechanism for this feedback inhibition was not clear, although it had been shown previously in transgenic mouse studies that an activated immunoglobulin transgene could allelically exclude the endogenous genes in most transgenic B cells. Immunoglobulin heavy chain genes encode two mRNAs, one for secreted and one for membrane-bound antibody, and more recently it had been shown that a transgene producing only the secreted form does not mediate allelic exclusion. The work reported here completes the circle, by showing that a transgene that produces only the membrane-bound immunoglobulin is sufficient to cause allelic exclusion, and that this exclusion is tighter than that observed with the transgene making both membrane-bound and secreted forms.

#### Studies of DNA repair and aging

The focus of this study is to examine if alterations exist in the abilities of human cells to repair DNA damage. The emphasis of these studies will be to examine isolated cell populations that are functionally important to aging.

#### Effect of in vivo and in vitro aging on neoplastic transformation

The relationship between aging and carcinogenesis was explored by transforming cultured cells derived from various sources with oncogenes. To mimic the in vivo state, we prepared primary culture cells from lung and skin tissues. Young and old rats



were mainly used as donors. For in vitro studies fibroblasts from human fetal lung and rat whole embryos were passaged to appropriate population doublings. Cells were transfected with the calcium phosphate precipitated oncogene DNA then subjected to a focus assay. The number of foci, which indicate the number of transformed cells, were examined to determine if older cells respond differently to the oncogenes than younger cells. Our results indicate that cellular aging alters the intrinsic susceptibility to oncogene induced neoplastic changes at the cellular level.

#### Measurement of mutational events in cellular aging

The cellular aging process has been attributed to the accumulation of errors in cell control mechanisms with time. One possible and attractive hypothesis is that errors occurring in particular genes which control cell proliferation may cause cellular aging. To elucidate what type and amount of errors (mutations) are actually taking place in DNA molecules, we have introduced a shuttle vector pMCiI into early passage human diploid cells. By returning the vector to *E. coli*, we can estimate how many and what kind of mutations the vector has acquired in cultured cells.

#### Genetic fingerprinting

The recent discovery of polymorphic minisatellite DNA regions has made it possible to generate unique genetic "fingerprints" of individuals through Southern hybridization of genomic DNA. Since the bands produced in an individual fingerprint can be attributed to either that person's father or mother (i.e. the bands are transmitted in Mendelian fashion), the technique is most useful for studying linkage and segregation in samples from family pedigrees. These minisatellite DNA probes can also be utilized to determine genetic linkage to diseases such as Alzheimer's disease. Currently, we are examining a large Alzheimer family to determine if there is any linkage between certain "fingerprint" bands and the Alzheimer gene(s).





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00700-01 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Genetic Fingerprinting

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P. I.: E. L. Schneider Acting Branch Chief

others: J. White Research Associate

## COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA, (C. Gerald McCleaver,  
Penn State University.

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

.1

## OTHER:

.9

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The recent discovery of polymorphic minisatellite DNA regions has made it possible to generate unique genetic "fingerprints" of individuals through Southern hybridization of genomic dna. Since the bands produced in an individual fingerprint can be attributed to either that person's father or mother (i.e. the bands are transmitted in Mendelian fashion), the technique is most useful for studying linkage and segregation in samples from family pedigrees. These minisatellite DNA probes can also be utilized to determine genetic linkage to diseases such as Alzheimer's disease. Currently, we are examining a large Alzheimer family to determine if there is any linkage between certain "fingerprint" bands and the Alzheimer gene(s).



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00701-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Studies of DNA repair and aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	E.L. Schneider	Acting Chief	LMG, NIA
Others:	N.P. Singh	Visiting Associate	LMG, NIA
	D.B. Danner	Senior Staff Fellow	LMG, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.2

## PROFESSIONAL:

1.2

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- |   |  |                                      |
|---|--|--------------------------------------|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

The focus of this study is to examine if age-dependent alterations exist in the abilities of human cells to repair DNA damage. The emphasis of these studies will be to examine isolated cell populations that are functionally important to aging.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00702-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Effect of In vivo and in vitro Aging on Neoplastic Transformation

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - E.L. Schneider, Acting Chief, LMG, NIA  
Others - T. Kunisada, Fogarty Fellow, LMG, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

1.0

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The relationship between aging and carcinogenesis was explored by transforming cultured cells derived from various sources with oncogenes. To mimic the in vivo state, we prepared primary culture cells from lung and skin tissues. Young and old rats were mainly used as donors. For in vitro studies fibroblasts from human fetal lung and rat whole embryos were passaged to appropriate population doublings. Cells were transfected with the calcium phosphate precipitated oncogene DNA then subjected to a focus assay. The number of foci, which indicate the number of transformed cells, were examined to determine if older cells respond differently to the oncogenes than younger cells. Our results indicate that cellular aging alters the intrinsic susceptibility to oncogene induced neoplastic changes at the cellular level.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00703-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
for Decreased Immune Function in Aging Humans and Rats

Molecular Basis

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA

Others - Edward L. Schneider, Acting Chief, LMG, NIA

Mike McCoy, Research Associate, LMG, NIA

## COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, Clinical Immunology Section,  
NIA (Drs. William Adler and James Nagel)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.3

## PROFESSIONAL:

.3

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

It is well established from human and animal studies that there is a general decrease in immune function that occurs with aging. This project focuses on examining the cause(s) for this decline at the molecular level. In particular, we have focused on the activation of T lymphocytes by mitogen. Three T-cell proteins have been examined thus far: interleukin 2 (IL-2), a lymphokine absolutely required for the proliferation of certain T cell populations; IL-2 receptor (IL-2R), the cell surface receptor for IL-2; and interferon gamma, another lymphokine whose regulation is intimately linked to IL-2. Expression of the IL-2 and IL-2R genes in human peripheral blood lymphocytes (PBL) was examined from 13 young and 17 elderly donors. In addition to decreased proliferative capacity, elderly individuals displayed a significant decrease in the amount of IL-2 protein activity and expression of IL-2R relative to younger individuals. These decreases were accompanied by decreased levels of IL-2 and IL-2R specific mRNA. Similar results have been obtained with interferon gamma in a smaller number of donors. Thus, it appears that decreased induction of all three of these genes upon antigenic stimulation contributes to the diminished T cell function observed in the elderly.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00704-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Molecular Genetic Analysis of Alzheimer's Disease

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	J. Milecki	Visiting Scientist	LMG, NIA
	E.L. Schneider	Acting Chief	LMG, NIA

## COOPERATING UNITS (if any)

Dementia Research Service, Division of Chronic and Degenerative Diseases, Cornell Medical College (J. Blass, R. Shue)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

0.7

## PROFESSIONAL:

0.7

## OTHER:

0.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews

☐ (b) Human tissues☐ (c) Neither

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Dr. John Blass at Cornell has shown that the activity of three thiamine-dependent enzymes--transketolase, alphaketoglutarate dehydrogenase, and pyruvate dehydrogenase--are decreased in two dementias, Wernicke-Korsakoff Syndrome and Alzheimer's disease. In general, this decrease occurs in body tissues not directly affected by the disease process; this suggests that inactivation of these enzymes is not simply an effect of the underlying pathology but may be intimately related to the cause of each disease, perhaps directly or perhaps as a predisposing factor. The goal of this project is to clone the genes for these enzymes, beginning with transketolase, by screening cDNA expression libraries from human brain and liver with antibodies made by the Blass group and with synthetic oligonucleotides whose sequence will be derived from microsequencing of purified protein provided by the Blass group. The cloned DNAs for these genes will then be used as probes to analyze the structure and function of the genes in Alzheimer and Wernicke patients versus normal controls.

We have also completed a small pilot experiment to analyze Alzheimer brain for reverse transcriptase, in order to ask if a retrovirus might play a role in this disease.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00705-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cloning of a gene involved in shutting off cell growth.

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	Mark Nuell	Staff Fellow	LMG, NIA
	E.L. Schneider	Acting Chief	LMG, NIA

## COOPERATING UNITS (if any)

Dept. of Virology, Baylor College of Medicine (J.R. Smith)  
Noble Foundation, Ardmore, Oklahoma (K. McClung)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute of Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.3

## PROFESSIONAL:

1.3

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- |   |  |                                      |
|---|--|--------------------------------------|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

Smith has shown that when poly(A)+ RNA derived from human diploid fibroblasts at late passage is microinjected into the same cell type at early passage, the growth of the early passage cells is halted. A functionally identical activity derived from rat liver (by K. McClung and J. Smith) has a single molecular weight peak of activity on sucrose gradients. These data suggest that a single messenger RNA has the ability to shut off cell growth, and dilution experiments suggest that the message is abundant (1/100-1/1000 of total message). We plan to clone this mRNA by hybrid selection screening of a cDNA library, and then to analyze the structure and expression of the gene.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00706-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders) Transcriptional Control Elements in the Gibbon Ape Leukemia Virus, LTR

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA  
Others - Jennifer Luethy, Research Associate, LMG, NIA

## COOPERATING UNITS (if any)

Laboratory of Pathology, NCI (Dr. David Levens)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.8

## PROFESSIONAL:

.25

## OTHER:

.5

## CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided)

Studies were undertaken to localize precisely the transcriptional enhancer elements within the long terminal repeats (LTRs) of different gibbon ape leukemia virus (GALV) strains and identify the cellular factor which binds to the enhancer region.

1) We have shown that the major element responsible for enhancer activity of the GALV LTR is contained within a 12 bp sequence of a 45 bp repeated DNA segment.

2) Using exonuclease II and DNase I footprinting techniques we have identified a nuclear factor which binds specifically to the 12 bp enhancer sequence. It is present in cells which express GALV but not in cells which express GALV poorly.

3) We have demonstrated that the tumor promoter phorbol myristate acetate can enhance transcriptional activity of the GALV LTR 50-100 fold in various lymphoid cell lines. It also enhances expression of several other viral transcriptional elements including SV40, human T cell lymphotropic virus type I, and Rous sarcoma virus, suggesting it works via a generalized mechanism. For practical purposes, PMA provides a convenient means for increasing transient expression of foreign DNA in lymphoid cells.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00707-01 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of

Interleukin 2 Gene Expression in Lymphoid and Nonlymphoid Cells

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

P.I. Nikki Holbrook, Senior Staff Fellow, LMG, NIA

Others - Jennifer Luethy, Research Associate

## COOPERATING UNITS (if any)

Alberto Gulino, Dipartimento di Medicina Spermentale, Universita  
"LaSapienza", Roma, Italy

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.8

## PROFESSIONAL:

.25

## OTHER:

.5

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is focused at understanding the basic control mechanisms responsible for expression of the human interleukin 2 (IL-2) gene. Particular items addressed are as follows: 1) Expression of the human IL-2 gene in various cell types - Ordinarily, human IL-2 is expressed only in T cells where it is under tight inducible control. We have stably transfected the human IL-2 gene into mouse fibroblasts and a human epithelial cell line. In both cases the gene is constitutively expressed. The expressed mRNA is not of the expected size, however. RNA mapping experiments have been used to define the basis for its altered expression. 2) The mechanism for activation of IL-2 expression in MLA 144 cells by a retroviral insertion - The role of the viral-regulatory elements in influencing IL-2 expression in transient systems have been investigated. 3) Role of 3' sequences in controlling IL-2 expression have been examined.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00708-02 LMG

PERIOD: October 1, 1986 to September 30, 1987

PROJECT (80 characters or less. Title must fit on one line between the borders.)  
Identification of age-related transcripts in the mouse

INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

I.: D.B. Danner Senior Staff Fellow LMG, NIH  
Others: J. Wagner MacArthur (Summer) Research Fellow LMG, NIH

GRANTING UNITS (if any)

BRANCH: Laboratory of Molecular Genetics  
DIVISION

INSTITUTE AND LOCATION: National Institute on Aging, NIH, Baltimore, MD 21224

ESTIMATED MAN-YEARS: 0.5

PROFESSIONAL: 0.2

OTHER: 0.3

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews

☐ (b) Human tissues

☐ (c) Neither

SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

We are searching for messenger RNA's that are differentially expressed during the lifespan of mice. Our approach to this analysis is to make cDNA libraries from young (3 month) and old (27 month) mice from the GRC colony. These libraries will be compared by hybridization techniques to see what RNA messages are present in high copy in one library but not in another. The structure and tissue-specific expression of these messages will then be examined.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00709-02 LMG

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of changes in hormone expression with age

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	D.B. Danner	Senior Staff Fellow	LMG, NIA
Others:	David Stewart	Research Associate	LMG, NIA

## COOPERATING UNITS (if any)

Laboratory of Clinical Physiology, NIA (S.M. Harman,  
M. Blackman); Laboratory of Cellular and Molecular Biology, NIA  
(G. Roth).

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.2

## PROFESSIONAL:

0.2

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- |   |  |                                      |
|---|--|--------------------------------------|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |                                      |
| <input type="checkbox"/> (a2) Interviews    |  |                                      |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Harman and Blackman, LCP, NIA have shown that basal and stimulated levels of luteinizing hormone decline with age in the rat pituitary, and Roth, LCMB, NIA has shown that basal and stimulated levels of prolactin increase in the same system. We will be asking the question whether these age-related hormone changes are reflected in the level of messenger RNA produced by the hormone genes. This will be done by quantitative hybridization analysis of pituitary messenger RNA using cloned hormone gene probes. If message levels are altered, we will proceed to ask whether the changes are at the level of the gene or in the regulatory pathway controlling the gene. This will be done by assaying the expression of a control exogenous hormone gene in the environment of the old and young cell. This analysis should ultimately allow us to pinpoint the defect that aging produces in this regulatory circuit, and may have implications for the effect of aging on other regulated genes.



DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE  
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00710-01 LMG

PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Isolation of  
Genes Differentially Expressed in Brain of Old and Young Rats

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I. - Nikki J. Holbrook, Senior Staff Fellow, LMG, NIA  
Others - Joseph Fargnoli, Senior Staff Fellow, LMG, NIA  
Michael Blake, IRTA Fellow, LMG, NIA

COOPERATING UNITS (if any)

Laboratory of Radiation Oncology, NCI (Dr. Albert J. Fornace,  
Jr.)

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

TOTAL MAN-YEARS:

1.7

PROFESSIONAL:

1.6

OTHER:

.1

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews

☐ (b) Human tissues

☐ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Despite the structural, and biochemical changes reported to occur in aging brain, the mechanism(s) underlying the aging process itself remain unknown. Thus, we have begun a new project designed to explore differential gene expression in old and young rat brain. Using subtraction hybridization techniques we are attempting to clone genes which are differentially expressed in aged (24 month) and mature young (5 month) rats. Briefly, the basic approach is to construct two cDNA libraries; one from poly A+ RNA from young rats, the other from poly A+ RNA from old rats. Poly A+ RNA from one age group is hybridized to the cDNA derived from the opposite age group and the cDNA/mRNA hybrids removed. As a result, nonhybridizing cDNAs obtained and subsequently packaged in a bacterial vector, should be enriched or highly specific for a particular age group. Ultimately, this will give us the opportunity to identify and study those genes which are involved (associated) with the aging process in brain by virtue of their increased expression (or conversely, by their relative inactivity) at specific ages.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00711-01 LMG

## PERIOD COVERED

October 1, 1986 to March 31, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analysis of allelic exclusion in transgenic mice

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)

PI: D.B. Danner

Senior Staff Fellow

LMG, NIA

## COOPERATING UNITS (if any)

Department of Genetics, Harvard Medical School (MC Nussenzweig, AC Shaw, E Sinn, and P Leder). Laboratory of Immunopathology, NIAID, NIH (KL Holmes and HC Morse III).

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore MD 21224

## TOTAL MAN-YEARS:

0.1

## PROFESSIONAL:

0.1

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects  
☐ (a1) Minors  
☐ (a2) Interviews

☐ (b) Human tissues☐ (c) Neither

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Allelic exclusion is the process by which antibody-producing cells (B cells) shut down or exclude from expression one of their two antibody genes after they have started expressing the first. This selectivity is critical to an effective immune response, since it allows each clone of B cells to respond to one particular antigen. The mechanism for this feedback inhibition was not clear, although it had been shown previously in transgenic mouse studies that an activated immunoglobulin transgene could allelically exclude the endogenous genes in most transgenic B cells. Immunoglobulin heavy chain genes encode two mRNAs, one for secreted and one for membrane-bound antibody, and more recently it had been shown that a transgene producing only the secreted form does not mediate allelic exclusion. The work reported here completes the circle, by showing that a transgene that produces only the membrane-bound immunoglobulin is sufficient to cause allelic exclusion, and that this exclusion is tighter than that observed with the transgene making both membrane-bound and secreted forms.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00712-01 LMG

## PERIOD COVERED

July 1, 1987 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Direct Measurement of Mutational Events in the Cellular Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I. - Edward L. Schneider, Acting Chief, LMG, NIA  
others - T. Kunisada, Fogarty Fellow, LMG, NIA  
D. Miller, Guest Researcher, LMG, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Molecular Genetics

## SECTION

## INSTITUTE AND LOCATION

National Institute on Aging, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.02

## PROFESSIONAL:

.02

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The cellular aging process has been attributed to the accumulation of errors in cell control mechanisms with time. One possible and attractive hypothesis is that errors occurring in particular genes which control cell proliferation may cause cellular aging. To elucidate what type and amount of errors (mutations) are actually taking place in DNA molecules, we have introduced a shuttle vector pMCiI into early passage human diploid cells. By returning the vector to E. coli, we can estimate how many and what kind of mutations the vector has acquired in cultured cells.



**Annual Report of the Laboratory of Neurosciences**  
**National Insitute on Aging**

The Laboratory of Neurosciences (LN) at the National Institute on Aging was formed in 1978, and has embarked on a program of research on the central and peripheral nervous systems in health, aging and disease, including dementia. The Laboratory is located at the Clinical Center in Bethesda, Maryland, and is divided into two sections -- a Clinical Section on Brain Aging and Dementia, and a Basic Section on Cerebral Physiology and Metabolism. The Clinical Section is directed by Dr. Robert Friedland. In September 1982, a six bed patient care unit was established for an inpatient program to study patients with Alzheimer's and other dementias as well as normal subjects. The unit has use of the 12E ward in the Clinical Center. An Outpatient Dementia Clinic was started in 1982 to screen subjects for inpatient protocols and to establish methods for the differential diagnosis and staging of the various dementias.

This report summarizes the following projects: (A) Brain function in aging and dementia, (B) Functional interactions between brain regions, (C) Neuropsychology in aging and dementia, (D) Brain anatomy in aging and dementia, (E) Cerebrospinal fluid chemistry in aging and dementia, (F) Cerebral metabolism, relation to brain function and aging, (G) Brain lipid metabolism, relation to function and aging, (H) Molecular biology of brain aging and disease, (I) Blood-brain barrier and central nervous system functions, (J) Brain nutrients and metals in aging and disease, (K) Regulation of neuronal development, and (L) Function and structure of peripheral nerve.





## A. Brain Function in Aging and Dementia.

1. Healthy aging. The effect of cerebral atrophy on cerebral metabolic rates for glucose (CMRglc), as determined with positron emission tomography (PET), was examined in 49 healthy men aged 21-83 years, under resting conditions with eyes covered and ears plugged. Cerebral atrophy was estimated using quantitative CT by methods described Section F. Atrophy, indicated by increased CSF volume, was correlated with global CMRglc, but accounted for no more than 13% of the variance. CMRglc, uncorrected or corrected for CSF volume, was age-invariant, indicating that in the absence of disease, compensatory mechanisms in the senescent human brain counteract effects of morphological and neurochemical age changes. This work was done by N. Schlageter and B. Horwitz.

2. Dementia of the Alzheimer type (DAT). Haxby et al. (1985) demonstrated left-right asymmetries of rCMRglc in a cross-sectional study of DAT. In a longitudinal study with a mean test/retest interval of 15 months, there was no significant change in any metabolic asymmetry measure over time, nor in the correlation between metabolic asymmetry and neuropsychological abnormalities. Thus, functional cerebral asymmetries are stable in individual DAT patients, suggesting that they arise from a progressive organic disorder. This work was conducted by C. Grady and J. Haxby.

Course of DAT. A longitudinal analysis of mildly demented DAT patients showed that memory deficits are the first neuropsychological impairments to occur, followed by problems with attention to complex cognitive sets and abstract reasoning, which are followed in turn by deficits in language and visuospatial abilities. Neocortical metabolic abnormalities usually precede impairment of neocortically mediated attention and abstract reasoning by 8 to 16 months, and precede impairment of neocortically mediated language and visuospatial function by 12 to 37 months. PET can be used to characterize early DAT prior to the appearance of neocortical deficits and dementia. This work was conducted by C. Grady and J. Haxby.

3. Aging and Down syndrome. We measured rCMRglc with PET in young adult Down subjects aged 19-33 years, and Down subjects older than 48 years. Mean CMRglc was significantly less in the older than the younger subjects. rCMRglc values in the parietal and temporal lobes were specifically reduced, compared to rCMRglc in the sensorimotor cortex, as we have reported for DAT. All the older Down subjects also had poorer cognitive skills than did the younger subjects, and half were demented on behavioral assessment. An age decline in both cerebral metabolism and cognitive function in Down syndrome, corresponding to the appearance of Alzheimer pathology, indicates that Down syndrome is a model for Alzheimer disease. This work was directed by M. Schapiro.

## B. Functional Interactions between Brain Regions.

1. Patterns of brain metabolism in healthy men. A matrix method was developed to examine functional interactions between brain regions, by correlating regional cerebral metabolic rates for glucose (rCMRglc), as



determined with PET, under reduced visual and auditory stimulation. Brain regions in one cerebral hemisphere were metabolically correlated with homologous regions in the other, reflecting functional connections via the corpus callosum. Regions in the frontal and parietal lobes were closely coupled with each other, but not with regions in the temporal and occipital lobes, which formed an independent coupled unit. At rest in healthy men, the brain demonstrates left-right regional metabolic coupling and, within each hemisphere, two independent interacting units, the frontal-parietal and occipital-temporal areas. Matrix analysis provides another way in addition to absolute metabolic rates to examine brain functional activity. This work was directed by B. Horwitz.

2. Metabolic pattern in dementia of the Alzheimer type (DAT). rCMRglc values obtained with PET were correlated pairwise, according to the method of Horwitz et al. (1986), for a group of 21 mostly mildly to moderately demented DAT patients and 21 age-matched controls. The DAT group differed significantly from controls in showing a loss of correlations between frontal and parietal lobes, and a loss of significant correlations between homologous right and left hemispheric regions. The loss of homologous correlations suggests disconnection between the right and left hemispheres in DAT, whereas the loss of ipsilateral correlations suggests hemispheric dysfunction. This work was performed by B. Horwitz.

### C. Neuropsychology in Aging and Dementia.

1. Healthy aging. J. V. Haxby demonstrated, in 40 healthy men aged 21 to 83 years, that age differences in performance on tests of general intelligence (Wechsler Adult Intelligence Scale) and of visual memory (Benton Visual Retention Test) were significantly less than differences reported in normative studies with these tests, suggesting that increasing prevalence of illness in the elderly contributes to age-related differences in normative standards for neuropsychological tests. Performance was not correlated significantly with regional cerebral metabolic rates for glucose (rCMRglc), as measured with PET. This lack of correlation supports the hypothesis that physiological and psychological cerebral functions are coupled only when both are under the limiting influence of disease.

Selected memory loss. In 60 healthy men, language abilities were preserved while visuospatial performance was reduced in relation to age. A similar distinction was found for memory capacities. Memory for verbal material showed no significant age difference, whereas memory for visuospatial material declined. These results suggest that verbal memory is preserved in the healthy elderly, whereas visuospatial performance and visuospatial memory are reduced. This work was done by E. Koss and J. Haxby.

Metabolic-cognitive correlations. In patients with moderate DAT, the relative disproportion of language and visuospatial impairments was correlated with right-left asymmetry of rCMRglc. Moreover, discrepancies between calculations or immediate visuospatial memory span, on the one hand, and attention or verbal fluency, on the other, correlated significantly with metabolic discrepancies between parietal and premotor association cortices. Heterogeneity of neocortically mediated neuropsychological deficits in moderate DAT is related to the topographical distribution of cortical metabolic deficits. This work was directed by J. V. Haxby.



2. Down syndrome. Cognitive decline. Six older subjects (age 39 to 64 yr) with Down syndrome performed significantly worse than 23 younger subjects (age 21 to 34 yr), on tests of word knowledge, visuospatial construction, immediate memory for visuospatial location, and recognition memory for visual shape. There was no overlap between the younger subjects and the 5 subjects over age 45 on most tests, unlike age-related differences in healthy controls. Age-related cognitive differences in Down syndrome probably reflect the appearance of Alzheimer neuropathology. This work was conducted by J. V. Haxby and M. Schapiro.

#### D. Brain Anatomy in Aging and Dementia.

1. Quantitative analysis of CT data. Methods. A computerized procedure was developed to quantify the volumes of cerebral cortical structures from data obtained with computerized transverse axial tomography (CT). By means of an image processing procedure, the means and standard deviations of CT densities (Hounsfield units) of representative cerebrospinal fluid, white matter and gray matter were determined for each CT scan, the number of volume units ascribed to each tissue type was estimated, and the net tissue volume summed of consecutive scans was determined. Regions of interest were outlined by a light pen in each scan and volumes were calculated by summation over serial scans.

2. DAT: longitudinal studies. Men and women with DAT and controls were studied over 6 months to 5 years with serial quantitative CT. In the male patients, mean rates of enlargement of third ventricle volume and of total lateral ventricular volumes exceeded those in controls. Female DAT patients also had significantly high rates of ventricular enlargement. There was only 5% overlap between the rates of lateral ventricular enlargement in DAT patients and controls. Rates of neuropsychological decline correlated with rates of ventricular enlargement. These results indicate that longitudinal quantitative CT studies can be used to distinguish DAT from control subjects. This work was done by J. Luxenberg.

#### E. Cerebrospinal Fluid Chemistry in Aging and Dementia.

1. Corticotropin releasing hormone (CRH) in DAT. CRH is a 41-amino acid peptide which is present in the hypothalamus, amygdala and substantia innominata, regions which are pathological in Alzheimer's disease. CRH concentrations were determined in extracted CSF from 33 DAT patients and 13 controls. The DAT patients showed a significant reduction in concentration as compared with controls, 24.8 pg/ml as compared with 35.2 pg/ml. Moreover, the mean CSF concentration of ACTH was less in the DAT patients, 24.4 pg/ml as compared with 30.6 pg/ml in controls, demonstrating involvement of CRH-containing neurons in DAT. This work was directed by C. May.

2. Peptidyl-a-amidation activity in DAT. The peptidyl-a-amidation enzyme (PAM) is coreleased from secretory granules with amidated peptides, including CRH. PAM activity was significantly reduced in CSF of DAT patients as compared with controls, further suggesting that there is a selective loss or dysfunction in DAT of brain neurons which produce amidated neuropeptides. This work was directed by C. May.

3. CSF biopterin in DAT. Tetrahydrobiopterin is a cofactor in the hydroxylation of phenylalanine, tyrosine and tryptophan, leading to the eventual





synthesis of the monoaminergic neurotransmitters, dopamine, norepinephrine and serotonin, respectively. Total bipterin concentration was significantly reduced in the CSF of 30 patients with DAT (13.5 pmol/ml) as compared with 19 controls (18.9 pmol/ml), suggesting a central bipterin and monoamine deficiency in DAT. This work was performed by A. Kay and S. Kaufman.

4. CSF monoamines in DAT with extrapyramidal features (EDAT). Monoamine metabolites and bipterin in lumbar CSF were determined in DAT patients with (EDAT) and without extrapyramidal signs, and in controls. The concentrations of bipterin and of homovanillic acid were significantly less in the EDAT patients than in either the DAT patients or controls, suggesting that EDAT patients have a specific bipterin-dopaminergic central deficiency as compared with DAT. This work was conducted by J. Kaye and C. May.

#### F. Cerebral Metabolism, Relation to Brain Function and Aging.

1. Cerebral blood flow in Beagles of different ages. Regional cerebral blood flow (rCBF), a measure of functional activity, was measured in Beagles by the i.v. infusion of  $^{14}\text{C}$ -iodoantipyrine, in relation to age. Lower values at 12 than at 1 year of age were statistically significant only in 9 of 35 brain regions, and ranged from -11% to -25%. Most brain regions showed reductions by an average of 29% in the 14- to 15-yr-old dogs, which demonstrated cardiovascular and sensorimotor disease. Thus, cerebral functional activity is minimally reduced during most of the adult life of the dog, but falls in extreme senescence in relation to disease. This work was conducted by H. Tabata.

2. Cholinergic function and age. Male Fischer-344 rats, aged 3 or 24 months, were administered arecoline and rCMRglc was measured as noted above. Cerebral metabolic responses did not differ significantly between the two age groups, indicating that muscarinic post-synaptic receptor responses are intact in the senescent rat brain. This work was conducted by G. Pizzolato and T. Soncrant.

3. Dopaminergic system and age. Peak metabolic effects of haloperidol were significantly less in 33 mo old than rats than in 3-mo and 12-mo-old Fischer 344 rats. Catalepsy also was less catalepsy was less in response to haloperidol in older animals. However, brain concentrations of haloperidol were higher in old than in young rats, due to a slower elimination. These age differences are consistent with reduced brain dopaminergic markers in old rats, and suggest an imbalance between dopaminergic and cholinergic activity. This work was conducted by G. Pizzolato and T. Soncrant.

#### G. Brain Lipid Metabolism, Relation to Function and Aging.

1. Jpalm in the developing rat. Jpalm was measured in awake Fisher-344 rats between the ages of 15 days and 3 months. Jpalm rose between 15 and 20 days of age, in gray and white matter regions, then declined 4-5 fold in gray matter and 7-10 fold in white matter by 38 days, and reached adult levels by 3 months. The white/gray ratio for Jpalm declined significantly between 20 days and adulthood. The time course of Jpalm corresponds to the time course of brain myelination and growth during development of the rat. Jpalm clearly is a measure of brain lipid synthesis during brain development. This work was performed by H. Tabata.





2. Entry of plasma 14C-palmitate into brain metabolic pools. The distribution of radioactivity in brain metabolic pools, following the intravenous injection of [U-14C] palmitate in awake rats, was measured to examine intermediate metabolism of plasma-derived palmitate. At 4 hour post injection, most brain radioactivity was in lipids, mainly phospholipids, and in protein, with some in the aqueous aspartate and glutamate pools. Net brain radioactivity did not differ between 4 hour and 24 hour, supporting the argument that 4 hour radioactivity is equivalent to 14C-palmitate which has been incorporated into stable brain structures. This study contributes to the understanding of intermediate compartments in the Jpalm model, and was conducted by J. Miller and J. Gnaedinger.

#### H. Molecular Biology of Brain Aging and Disease.

Aging and brain protein synthesis. J. Cosgrove, using the cell free system, demonstrated age invariance of brain protein synthesis capacity, and no age difference in the aggregation state of polyribosome profiles obtained from brains of 3-mo and 34-mo-old Fischer-344 rats. These results agree with reports from this laboratory that brain oxidative metabolism and palmitate incorporation generally are age invariant in the Fischer-344 rat, and point to compensatory mechanisms that maintain cerebral overall cerebral metabolism during healthy aging.

#### I. Blood-Brain Barrier and Central Nervous System Function.

##### 1. Reversible osmotic opening of the blood-brain barrier.

a. Pore mechanism for BBB opening. To further support the tight junctional as compared to the transcellular channel or vesicular mechanism, B. Armstrong and P. J. Robinson examined the time course of cerebrovascular permeability to nonelectrolytes of different size, 14C-sucrose (mol. wt. = 340 daltons), and 3H-dextran (mol. wt. 200,000), following osmotic barrier opening. Whereas the barrier was opened to both radiotracers immediately following the intracarotid injection of 1.8 molal arabinose solution in rats, the rate of closure was faster with the larger molecule. Size differentiation during recovery supports the tight junctional mechanism rather than the vesicular mechanism, as vesicles are much larger than any of the tracers and would not be selectively permeant to smaller as compared to larger molecules. Furthermore, the differential rate of barrier reclosure suggests that, if drugs are to be used with the osmotic procedure, they should be administered within a few minutes after hypertonic infusion.

2. Protein binding of drugs affect brain uptake. The blood-brain barrier is impermeant to proteins, so that binding of a drug to plasma proteins may hinder drug uptake by brain. Plasma protein content and binding can change in aging and disease. P. Robinson developed a mathematical model, based on experimental data, that describes the kinetics of binding to proteins and predicts brain uptake rates of various protein-bound drugs. The model includes association and dissociation rate constants for drug/protein complex. Drug uptake is determined mainly by the dissociation rate constant as compared to brain capillary transit time. The model explains absence of entry of bilirubin into the brain (slow dissociation) but entry of palmitate into brain (rapid dissociation), and contributes to the understanding of kernicterus in the newborn.



## J. Brain Nutrients and Metals in Aging and Disease.

### 1. Facilitated transport of large neutral amino acids.

Concentration-dependent uptakes into brain of 14 large neutral amino acids, measured in anesthetized rats with the brain perfusion technique, depend on a single high-affinity carrier system at brain capillaries. Each uptake is stereospecific, saturable and sodium-independent, and follows Michaelis-Menten kinetics. Affinity ( $1/K_m$ ) varies 700 fold between regions, and is related primarily to amino acid side chain hydrophobicity. At normal plasma concentrations, the neutral transport system is close to saturation, forcing each amino acid to compete for transport sites and making brain susceptible to imbalances in plasma concentrations caused by nutrition or disease. This work was done by Q. R. Smith.

2. Amino acid uptake and aging. The concentration-dependent brain uptake of cycloleucine, a model nonmetabolizable large neutral amino acid, did not differ between Fischer-344 rats aged 3 months and 24 months. The values for the Michaelis-Menten constants,  $K_m$  and  $V_{max}$ , also showed no significant difference. Lastly, the plasma concentrations of each of 9 neutral amino acids did not vary with age, except for a 50% increase in threonine in the old rats. Thus, contrary to previous reports, cerebrovascular transport of large neutral amino acids is age-invariant in the rat. As transport is coupled to brain protein synthesis, these findings support the finding by J. Cosgrove (Section K2) that brain protein synthesis is age-invariant in the rat. The work was done by Q. R. Smith.

### 3. Ionic homeostasis of the central nervous system.

a. Calcium transport. Ca transport into the central nervous system was examined in rats after acute and chronic changes in plasma Ca concentrations. Transfer coefficients for  $^{45}\text{Ca}$  uptake into brain and cerebrospinal fluid were not altered by acute plasma changes. During chronic hypo- or hyper-calcemia, however, the spinal fluid transfer coefficient was inversely related to plasma Ca concentration. Thus, Ca transport into the central nervous system is regulated at a barrier site (choroid plexus) in chronic but not acute changes in plasma Ca. The work was performed by V. A. Murphy.

b. Homeostasis of central nervous system calcium. Immature rats were made chronically hypo- or hyper-calcemic by being fed diets that contained deficient or excessive amounts of calcium. After 8 weeks on a diet, plasma ionized and total calcium concentrations were 45% lower in low-Ca fed rats and 25% greater in high-Ca fed rats than in controls. In contrast, brain Ca changed by less than 9% and cerebrospinal fluid calcium changed by less than 13% in the experimental animals. The results demonstrate homeostasis of central nervous system calcium, and indicate that the blood-brain barrier must contain regulatory sites for calcium. This work was done by V. Murphy.

## K. Regulation of Neuronal Development.

1. Membrane properties of neurons of trisomy 16 mice. Trisomy 16 in the mouse is a model for trisomy 21 (Down syndrome) in humans, as specific genes on murine chromosome 16 correspond to genes on human chromosome 21 which contribute to the Down phenotype. Experimental conditions were established to culture



dorsal root ganglia (DRG) and spinal cord neurons from fetal trisomy 16 and control mice. Intracellular electrodes were employed to measure both passive and active electrical membrane properties. Trisomic neurons had a faster rate of rise of the action potential (depolarization), and a faster rate of fall of the action potential (repolarization), than controls, resulting in a shorter overall action potential. Overproduction of products of genes on chromosome 16 in the mouse results in abnormal electrical properties of neurons during development. This work was done by C. Orozco.

2. Voltage activated conductances in trisomy 16 neurons. Two sodium conductances, a fast tetrodotoxin (TTX)-sensitive and a slow TTX-resistant conductance, were demonstrated in trisomy 16 and control mouse DRG neurons in culture, using a whole cell patch clamp technique. The slow TTX-resistant conductance was 3-4 times higher than the fast TTX-sensitive conductance, indicating that the action potential of fetal DRG neurons is sustained by the slow conductance. Both conductances were about 50% higher in trisomy 16 than in control neurons, accounting for the higher rate of depolarization of the action potential in trisomic neurons. This work was conducted by C. Orozco.

#### L. Function and Structure of Peripheral Nerve.

1. Blood-nerve barrier in experimental diabetes. Permeability-surface area (PA) products were determined with a quantitative in vivo injection technique at the blood-nerve barrier of the tibial nerve, and at the blood-brain barrier, of control and streptozotocin-induced diabetic rats. The PA to [<sup>14</sup>C]mannitol at the nerve was increased by 100% in diabetic animals compared with controls, but that PA at the blood-brain barrier was unaltered. The increased PA at the nerve was accompanied by marked edema and a 32% decrease in conduction velocity. Thus, diabetes affects capillary integrity at nerve but not brain, possibly accounting for the peripheral neuropathy that frequently is produced. This work was performed by E. Rechthand.

2. Blood-nerve barrier during Wallerian degeneration. The frog sciatic nerve was transected close to the spinal cord, and the integrity of capillaries and perineurium were examined in the distal segment, 20 to 40 mm below the lesion, from 1 week to 7 months thereafter. In the segment undergoing Wallerian degeneration, horseradish peroxidase was shown by electronmicroscopy to penetrate the nerve by 1 week, and capillary endothelium was seen to proliferate. By 6 weeks, capillary permeability had returned to normal. Endoneurial capillary permeability does not depend on the presence of neuronal tissue within the nerve sheath, but may depend on presence of Schwann cells and glia. This work was conducted by C. Latker.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00120-10 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Blood-Brain Barrier and Central Nervous System Function

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: S.I. Rapoport Chief LN, NIA  
 N.H. Greig Visiting Associate LN, NIA

Others: P.J. Robinson Associate Professor Univ. of Brisbane, Australia  
 W. R. Fredericks Biologist LN, NIA  
 B.K. Armstrong Biologist LN, NIA  
 D.J. Sweeney Chemist LN, NIA  
 Q. Smith Research Physiologist LN, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

3.0

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A model was developed to interpret the binding of drugs and physiological substances to plasma proteins to determine how this binding effects the brain uptake of highly bound substances. The model was applied to bilirubin to assess kernicterus in infants.

Melphalan, an anticancer alkylating agent, was measured in the blood and brain of rats and its pharmacokinetics determined. It enters the brain via an amino acid transport system at the blood-brain barrier; its entry is related to its plasma protein binding, which is concentration-dependent.

The blood-brain barrier could be opened in rats and mice by intracarotid infusion of a hypertonic arabinose solution. The rate of reclosure was related to the size of the intravascular tracer, indicating that tight junctions between cerebrovascular endothelial cells were modified. Reversible osmotic barrier opening was used to deliver interferon to the brain of rats.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00121-10 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Function and Structure of Peripheral Nerve

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. Rechthand	Senior Staff Fellow	LN, NIA
	C. Latker	Senior Staff Fellow	LN, NIA
	K.C. Wadhvani	Staff Fellow	LN, NIA

Others:	S. Sato	Investigator	Univ. of Kioo
	T. Sundqvist	Investigator	Univ. of Linkoping
	P. Robinson	Visiting Associate	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA

## COOPERATING UNITS (if any)

Univ. of Kioo, Tokyo; Univ. of Linkoping, Sweden; SUNY State Univ., NY; Univ. of Maryland; Key Pharmaceuticals, Miami, FL; Univ. of Colombo, Sri Lanka; US Uniformed Health Services, MD.

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

4.5

## PROFESSIONAL:

3.5

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Glucose transport into the rat tibial nerve from blood, across blood vessels of the nerve endoneurium, is by a facilitated transport system that demonstrates stereospecificity and saturation, and allows matching of transport and nerve metabolic demand.

Permeabilities of the blood-nerve barrier to ions and nonelectrolytes are low, indicating limited exchange between blood and nerve. However, the barrier does not regulate nerve calcium, which slowly equilibrates between nerve and blood during chronic hypocalcemia and hypercalcemia. Capillaries of the nerve vasculature become more permeant during experimental diabetes, resulting in a peripheral neuropathy in rats accompanied by edema.

Blood flow in the rat sciatic nerve, as measured with laser Doppler flowmetry, is not autoregulated during acute hypotension. Histochemical methods indicate adrenergic innervation of blood vessels on the surface of the nerve, but not in the endoneurium.

Vesicular profiles are demonstrated in the perineurium of frog nerve and in endothelial cells of pial blood vessels, using rapid freezing and freeze substitution methods, demonstrating that vesicles do not contribute to transcellular macromolecular transport. Alkaline phosphatase within vesicles indicate that they are microdomains for enzymatic activity. Wallerian degeneration alters the permeability of the blood nerve barrier tissues of the frog for 6 weeks before returning toward normal values.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00122-09 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pharmacology of Central and Peripheral Catecholaminergic Nervous Systems

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

All Investigators departed NIH.

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

0

## PROFESSIONAL:

0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Project terminated 1986.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00123-09 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Neuronal Development

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	C. Orozco	Visiting Associate	LN, NIA
	P. Caviedes	Visiting Fellow	LN, NIA
	J. Koistinaho	Visiting Fellow	LN, NIA

Others:	C.H. Latker	Senior Staff Fellow	LN, NIA
	J. DeGeorge	Senior Staff Fellow	LN, NIA
	M. Matocha	Staff Fellow	LN, NIA
	J.W. Cosgrove	Senior Staff Fellow	LN, NIA

## COOPERATING UNITS (if any)

Salk Institute, LaJolla, CA; Department of Neurobiology, University of Illinois; Department of Pediatrics, University of California at San Francisco; Centro de Estudios Cientificos de Santiago, Chile.

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

3.5

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects    ☒ (b) Human tissues    ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Membrane channels in the sarcoplasmic reticulum of striated skeletal muscle were shown to be selective for calcium using a patch clamp technique, and to have a voltage dependent conductance.

Spinal cord neurons cocultured with muscle cells induce a decrease in the incidence of slow hyperpolarizing after potentials following an overshoot of the action potential. A soluble factor released by these neurons, and causing this effect, was isolated, with a molecular weight of less than 4000 daltons.

Dorsal root ganglia (DRG) neurons from trisomy 16 mice, a model for trisomy 21 (Down syndrome) in humans, were maintained in tissue culture, and shown to have different electrical properties than control neurons. A faster action potential, with a higher rate of depolarization, was present in the trisomy 16 neurons. Similar differences were observed between trisomy 16 and control spinal cord neurons. With the patch clamp technique, a fast, tetrodotoxin-sensitive and a slow tetrodotoxin-resistant sodium conductance were shown in neurons from both type of embryos. Both conductances were higher in trisomy 16 compared to control neurons. A small channel with a single conductance of 2.7-2.2 pS was recorded in control neurons.

Human fetal DRG neurons with trisomy 21 show a shorter duration of the action potential compared to control neurons. Voltage clamp studies revealed a decreased activation time constant for outward potassium currents. As in fetal mouse DRG neurons, a fast tetrodotoxin-sensitive and a slow tetrodotoxin-insensitive Na current could be identified, the latter accounting for 90% of the total charge moving across the membrane.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00125-09 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebral Metabolism, Relation to Brain Function and Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T. Soncrant	Staff Fellow	LN, NIA
	G. Ricchieri	Visiting Fellow	LN, NIA
	U. Freo	Visiting Fellow	LN, NIA

Others:	S.I. Rapoport	Chief	LN, NIA
	E. McCann	Medical Staff Fellow	LN, NIA
	H.W. Holloway	Biologist	LN, NIA
	K.M. Wozniak	Visiting Fellow	LCS, NIMH

## COOPERATING UNITS (if any)

Department of Neuropathology, Univ. of Western Ontario;  
Laboratory of Clinical Sciences, NIMH, NIH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

5.0

## PROFESSIONAL:

3.0

## OTHER:

2.0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The regional cerebral metabolic rate for glucose,  $rCMR_{glc}$ , was measured with the 2-deoxy-D-glucose technique in 3 month and 24 month old male Fischer-344 rats, following administration of arecoline, a cholinergic agonist. The absence of age differences in most brain areas indicated that muscarinic post-synaptic receptor mechanisms are intact in the rat brain during aging.

Dopaminergic function in the rat brain was examined by measuring  $rCMR_{glc}$  in response to bromocriptine (a dopaminergic agonist) and sulpiride (a specific antagonist). The response to bromocriptine was reduced in senescent as compared to younger rats, suggesting a reduced central dopaminergic function, and an imbalance between cholinergic and dopaminergic systems.

Regional cerebral blood flow ( $rCBF$ ) was age invariant in awake Beagles between 1 and 12 years of age, and declined only in extreme senescence in relation to systemic disease, suggesting that cerebral functional activity is maintained during the life span of the healthy dog.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00126-08 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: R. Friedland	Chief, SBAD	LN, NIA
C. Grady	Research Psychologist	LN, NIA
M. Schapiro	Senior Staff Fellow	LN, NIA
B. Horwitz	Senior Staff Fellow	LN, NIA
A. Kumar	Medical Staff Fellow	LN, NIA

## COOPERATING UNITS (if any)

Child Psychiatry Branch, NIMH; Department of Nuclear Medicine, CC

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

2.3

## PROFESSIONAL:

2.3

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The regional cerebral metabolic rate for glucose (rCMRglc) was examined as a measure of cerebral functional activity in 49 healthy men between the ages of 21 and 83 years, by means of positron emission tomography (PET). Average hemispheric glucose utilization in individual regions of the right and left hemispheres did not decline significantly with age ( $p > 0.05$ ), even after correction for cerebral atrophy.

Asymmetry of cerebral metabolism in mildly and moderately demented Alzheimer's disease patients was shown to be unchanged and correlated with appropriate neuropsychological deficits over periods of up to 2 years. No significant relation between age at onset of dementia and neuropsychologic manifestations of AD was found when early and late onset patients were compared, although early onset patients had more severe parietal lobe hypometabolism. Longitudinal analysis of mildly demented patients demonstrated a systematic progression of neuropsychological deficits which were preceded by metabolic abnormalities by many months. Using a linear histogram method, ratios of peak rCMRglc in association cortex to peak rCMRglc in primary cortex were significantly reduced in mild and moderate-severe AD patients. These ratios also correlated significantly with dementia severity.

Regional cerebral metabolism was reduced in older as compared to younger adults with Down syndrome, as expected from the Alzheimer-type neuropathology in older Down subjects. Similarities between Alzheimer's disease and dementia and cognitive deterioration in Down syndrome were demonstrated.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00127-07 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurochemistry of the Brain in Relation to Aging and Neurodegenerative Disorders

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J. Atack	Visiting Fellow	LN, NIA
Others:	C. Franco-Hidalgo	Visiting Fellow	LNS, NIA
	D. Katz	Pathologist	CC, NIH
	M. Ball	Neuropathologist	Univ. W. Ontario,

## COOPERATING UNITS (if any)

Department of Behavioral Sciences, Johns Hopkins Medical School, Baltimore;  
Department of Neuropathology, University of Western Ontario, Canada;  
Department of Pathology, Clinical Center, NIH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.0

## PROFESSIONAL:

2.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Following lesions of the rat nucleus basalis of Meynert, there was an acute (1 week) increase in the number of M2 muscarinic binding sites which returned to normal after 3 months. On the other hand, M1 muscarinic receptors were normal at 1 week but decreased at 3 months. These changes were bilateral despite the lesion being unilateral. These results suggest that there are complex changes in cortical cholinergic receptors following degeneration of cortical cholinergic input.

Nerve growth factor (NGF) receptors were identified in the human cerebral cortex and had a dissociation constant (Kd) very similar to the cholinergic-specific NGF receptors recently described in the rat brain.

Autoradiographic methods were established to identify receptor binding sites in large sections of the human brain.

Procedures were established to obtain rapid autopsies on inpatients and outpatients who die, and for preparing brain tissue for diagnosis and chemical and neurochemical analysis.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00128-07 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Analytical Drug Methods

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Sweeney	Chemist	LN, NIA
	J. Kusmierz	Visiting Fellow	LN, NIA

Others:	E. Daly	Chemist	LN, NIA
	S. I. Rapoport	Chief	LN, NIA
	C. May	Medical Staff Fellow	LN, NIA
	A. Broosi	Chief	LC, NIADDK

## COOPERATING UNITS (if any)

A. Broosi, NIADDK, NIH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- |   |  |   |
|---|--|---|
| <input type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input checked="" type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors        |  |   |
| <input type="checkbox"/> (a2) Interviews    |  |   |

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Analytical methods using high performance liquid chromatography with ultra-violet detection were developed for the measurement of eseroline, a physotigmine metabolite, and for bromocriptine, a dopaminergic agonist, in plasma and brain of rats.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00129-07 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Nutrients and Metals in Aging and Disease

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: Q. R. Smith Research Physiologist LN, NIA  
 V. Murphy Staff Fellow LN, NIA  
 M. Aoyagi Visiting Fellow LN, NIA  
 T. Nagashima Visiting Fellow LN, NIA  
 H. Mori Visiting Fellow LN, NIA

Others: S. I. Rapoport Chief LN, NIA  
 B. W. Agranoff Professor Univ. of Michigan

## COOPERATING UNITS (if any)

Univ. of Michigan, MI; INSERM, Paris, France; Oak Ridge Associated Universities, TN; FDA, Rockville, MD; Tokyo Medical and Dental University, Tokyo, Japan.

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

4.0

## PROFESSIONAL:

4.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unrounded type. Do not exceed the space provided.)

Fourteen plasma neutral amino acids are transported into brain of the adult rat by a single high-affinity system at brain capillaries. Transport affinity differs among the amino acids by 700 fold and is determined primarily by amino acid side chain hydrophobicity. At normal plasma concentrations, the transport system is saturated; each amino acid must compete for available transport sites. Competition makes the brain susceptible to imbalances in plasma amino acid concentrations.

Neutral amino acid transport into rat brain decreases between 1 week and 3 months of age and then remains constant between 3 and 24 months. Changes in amino acid transport with age correlate with changes in brain protein synthesis. Amino acid transport is not induced or repressed by chronic hyperaminoacidemia.

The nonmetabolizable amino acid, 1-aminocyclohexanecarboxylic acid, is transported by the cerebrovascular neutral amino acid carrier and may be a suitable in vivo probe of amino acid transport in humans using positron emission tomography.

The kinetics of glucose transport across the blood-brain barrier can be described by a model with a single facilitated system. Accurate values of Vmax and Km were obtained for D-glucose, 2-deoxy-D-glucose and 3-O-methyl-D-glucose.

Calcium concentrations in brain and CSF are maintained within 10% of control values after chronic changes of up to 50% in plasma Ca concentration. The transfer coefficient for <sup>45</sup>Ca uptake into CSF is inversely related to plasma Ca concentration, demonstrating regulated transport of Ca at the blood-brain barrier.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00130-05 LN.

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neuropsychological Function in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.: J.V. Haxby Senior Staff Fellow LN, NIA

C.L. Grady Research Psychologist LN, NIA

E. Koss Senior Staff Fellow LN, NIA

Others: B. Sonies Speech Pathologist RM, CC

R. Parasuraman Cognitive Psychologist Catholic University

J. Heisey Psychologist LN, NIA

## COOPERATING UNITS (if any)

Rehabilitation Medicine Department, Clinical Center, NIH; Department of Psychology, Catholic University

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

2.25

## PROFESSIONAL:

2

## OTHER:

.25

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Neuropsychologically relevant mental abilities are studied in healthy men at different ages, in patients with clinically-diagnosed Alzheimer's disease, and in adults with Down syndrome at different ages. Tests are administered to evaluate intelligence, memory, language, visual attention, visuooperative and visuoconstructive ability, and perceptual-motor speed. Age-related differences in general intelligence, verbal memory, and visual memory in our sample of healthy men, ranging in age from 20 to 83 years, were found to be smaller than the differences reported in normative studies of non-health-screened adults. No significant age-related differences on verbal processing and memory were found. Age-related differences on visuospatial processing and memory were significant. In healthy adults, visual memory and the discrepancy between verbal and visuospatial ability were not correlated with regional cerebral metabolic rates for glucose (rCMRglc) as measured by positron emission tomography (PET) and 18-Fluorodeoxyglucose, but the discrepancy between visual and verbal memory was correlated with right-left parietal rCMRglc asymmetry. Neuropsychological patterns were correlated with neocortical rCMRglc patterns in patients with moderate Alzheimer's disease, but not in patients with mild Alzheimer's disease. Longitudinal study of mildly impaired patients, however, demonstrated that the development of neocortically-mediated neuropsychological impairments follows the appearance of significant neocortical rCMRglc abnormalities. Older Down syndrome adults perform worse on mental abilities tests than do younger subjects. Immediate verbal memory appears to be less affected by age in Down syndrome than are other abilities.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00131-05 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurological Function in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.:	C. Grady	Research Psychologist	LN, NIA
	J. Kaye	Medical Staff Fellow	LN, NIA

Others:	A. Grimes	Audiologist	CC
	A. Pikus	Audiologist	CC
	J.W. Renfrew	Psychologist	LN, NIA
	C. May	Medical Staff Fellow	LN, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

.8

## PROFESSIONAL:

.5

## OTHER:

.3

## CHECK APPROPRIATE BOX(ES)

- |  |  |                                      |
|--|--|--------------------------------------|
| <input checked="" type="checkbox"/> (a) Human subjects | <input type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors                   |  |                                      |
| <input type="checkbox"/> (a2) Interviews               |  |                                      |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Research was carried out on motor function in man in relation to aging. With the use of a patient activity monitor worn on the non-dominant wrist in 43 healthy men for a period of 9 days, it was demonstrated that average motor activity was lower in older individuals, primarily as a result of low activity during daytime hours. Weekend mean activity was significantly different than weekday mean activity only in the younger subjects as a result of young subjects sleeping later on weekends than during the weekday period. The monitor has been shown to be useful in quantifying nocturnal disturbances, such as wandering, in patients with Alzheimer's disease.

In patients with Alzheimer's disease, studies of central auditory function using both dichotic and degraded monotic tests showed that performance on the dichotic test was more difficult for the patients, compared to healthy controls. Only dichotic performance was related to measures of cerebral atrophy and glucose metabolism in the temporal lobes. Evoked potential latencies were not different in patients with Alzheimer's disease compared to controls.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00132-05 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Anatomy in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I. J. Luxenberg Medical Staff Fellow LN, NIA

J. Kaye Medical Staff Fellow LN, NIA

B. Horwitz Senior Staff Fellow LN, NIA

Others: R. Friedland Section Chief LN, NIA

S.I. Rapoport Laboratory Chief LN, NIA

S.E. Swedo Medical Staff Fellow LNC, NIMH

J. Rumsey Psychologist LNC, NIMH

## COOPERATING UNITS (if any)

LNC, NIMH, NIH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

1.0

## OTHER:

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Computer assisted tomography (CT), together with three dimensional image reconstruction procedures, demonstrated in 22 men and 17 women with dementia of the Alzheimer type (DAT) that the volume of cerebrospinal fluid is larger than in age and sex matched control subjects. The volume of gray matter was smaller in the DAT subjects than in controls. The technique also demonstrated ventricular enlargement in the male DAT patients corresponding to the severity of dementia. In healthy subjects, the men had larger volumes of cerebrospinal fluid, third and lateral ventricles than did the women. Gray matter and white matter volumes did not differ between sexes. On the other hand, there were no differences, as compared with age matched controls, in brain morphometrics for adults with autism and for young adults with Down syndrome (after data were normalized to height).

Twelve men and six women with DAT and twelve healthy male control subjects were studied over 6 months to 5 years with serial CT of the brain. In the male DAT patients, the mean rates of enlargement of third ventricle volume and of total lateral ventricular volumes differed significantly from zero and from respective control values. The female DAT patients also had significant rates of enlargement of the third and total lateral ventricles. There was no overlap between the rates of lateral ventricular enlargement in DAT patients and controls. In men with DAT, the rate of neuropsychological decline correlated with rate of enlargement of the third ventricle and the right lateral ventricle.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00133-05 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 Characters or less. Title must fit on one line between the borders.)

Clinical Pharmacokinetics, Pharmacodynamics and Therapeutics

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. Kaye Medical Staff Fellow LN, NIA

Others: C. May Medical Staff Fellow LN, NIA  
S. Kaufman Chief LNC, NIMH  
S. Milstien Research Chemist LNC, NIMH  
R. Potter Chief CP, NIMH  
J. Sanes Senior Staff Fellow HMC, NINCDS  
K. Midha Professor of Pharmacy U. of Saskatchewan

COOPERATING UNITS (if any) Laboratory of Neurochemistry, NIMH;  
Section of Clinical Psychopharmacology, NIMH;  
Human Motor Control Section, NINCDS;  
College of Pharmacy, University of Saskatchewan, Canada

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

## PROFESSIONAL:

## OTHER:

1

1

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Subcutaneous tetrahydrobiopterin was administered to 5 patients with dementia of the Alzheimer type. No gross change in neurologic examination or significant adverse effects were observed. Cerebrospinal fluid (CSF) drug and monoamine metabolite concentrations were evaluated.

Intravenous haloperidol was administered to two healthy subjects to test the dopamine system in aging. No significant adverse effects were seen. CSF monoamine metabolites, plasma haloperidol and prolactin concentrations and quantitative cognitive and motor tests are being evaluated.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00134-04 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Brain Lipid Metabolism, Relation to Function and Aging

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: J. Gnaedinger	Senior Staff Fellow	LN, NIA
J. DeGeorge	Senior Staff Fellow	LN, NIA
S. Yamazaki	Visiting Fellow	LN, NIA
Others: P. Robinson	National Research Fellow	U. of Queensland, Australia
J. Miller	Research Associate	U. of Texas Health Science Center at Dallas

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

4.75

## PROFESSIONAL:

3.50

## OTHER:

1.25

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects      ☐ (b) Human tissues      ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A method was developed to measure the rate of incorporation of palmitate, Jpalm, from plasma into different brain regions in the awake rat.

Jpalm did not change between 3 and 34 months of age, indicating that the rate of turnover of palmitate-containing brain lipids was unchanged. During development of the rat, the time course of Jpalm corresponded to the time course of myelination in the developing brain.

Jpalm fell in central auditory pathways following damage to the cochlea. Following a 5 minute period of bilateral ischemia, gerbils had reduced palmitate incorporation into the irreversibly damaged CA 1 region of the hippocampus but increased incorporation into reversibly affected regions.

Palmitate incorporation into the hypoglossal nucleus increased maximally 24 days after hypoglossal nerve axotomy. This increase correlated with regenerative processes. Following axotomies in which nerve endings were sealed, palmitate incorporation was decreased at 24-35 days.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00135-04 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Biology of Brain Aging and Disease

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M. Matocha Staff Fellow LN, NIA  
J.R. Atack Visiting Fellow LN, NIA

Others: J.W. Cosgrove Senior Staff Fellow NINCDs  
G. Yang International Research Fellow LN, NIA

## COOPERATING UNITS (if any)

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.25

## PROFESSIONAL:

2.25

## OTHER:

---

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Amino acid incorporation was measured in a cell-free protein synthesis system derived from the brains of male Fischer-344 rats of different ages. This system has the capacity to initiate protein synthesis in vitro. There was no significant correlation between protein synthesis and age.

Differential gene expression in the rat brain at the level of protein end-product was observed for a number of brain proteins, but the level of most brain proteins did not change with age. Differential gene expression also was observed for a number of brain mRNAs, but the majority did not change with age.

The expression of the cellular homologues of three nuclear related oncogenes, v-fos, v-myc and v-myb, was examined in the rat brain. Sequences related to v-fos and v-myc but not to v-myb were detected. The expression of these sequences did not change with aging. In addition, the levels of B-actin mRNA did not change with age.

Transcript levels of several proto-oncogenes were measured in brain and liver of rats by Northern blot hybridization analysis. An age-related increase in the level of c-myc mRNA in liver, but not brain, was observed. The levels of B-actin, c-sis, and c-src-related transcripts were age-invariant in both organs. The activity and relative levels of the pp60c-src protein in rat brain also were age-invariant.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00140-03 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cerebrospinal Fluid Chemistry in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	C. May	Medical Staff Fellow	LN, NIA
	J. A. Kaye	Medical Staff Fellow	LN, NIA
	S.I. Rapoport	Chief	LN, NIA
Others:	J. R. Atack	Visiting Fellow	LN, NIA
	I. Rainero	Guest Worker	LN, NIA
	M. B. Schapiro	Senior Staff Fellow	LN, NIA
	D. Sweeney	Chemist	LN, NIA
	E. Daly	Chemist	LN, NIA

## COOPERATING UNITS (if any)

Lab. Neurochemistry, NIMH; Biological Psychiatry Branch, NIMH; Clinical Pathology Dept., NIH; Department of Endocrinology, Johns Hopkins School of Medicine; Department of Pharmacology, University of Pittsburgh, School of Medicine; Department of Neurology, Massachusetts General Hospital

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia/Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

1.4

## OTHER:

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Cerebrospinal fluid (CSF) concentrations of homovanillic acid, 5-hydroxy indoleacetic acid, norepinephrine and 3-methoxy 4-hydroxyphenyl ethylene glycol did not differ significantly between patients with Alzheimer's disease and age matched controls, and were not correlated with age in healthy men. CSF concentrations of choline increased with age in healthy men, and were higher in young adults with Down syndrome than in age matched controls. CSF bipterin, a coenzyme for tyrosine and tryptophan hydroxylase, was lower in patients with Alzheimer's disease than in controls, and was correlated with concentrations of 5-hydroxy-indoleacetic acid and homovanillic acid. Subtypes of Alzheimer's disease were identified: dementia of the Alzheimer type with extrapyramidal signs (EDAT), and with myoclonus (MDAT). The reductions in CSF acetylcholinesterase and somatostatin found in Alzheimer's disease were also found in EDAT and MDAT. However, these latter groups have additional deficits in monoamine markers; EDAT and MDAT have reduced CSF levels of homovanillic acid and bipterin, and additionally, MDAT is characterized by reductions in 5-hydroxy-indoleacetic acid.

Corticotropin releasing hormone, a neuropeptide, was significantly reduced in the cerebrospinal fluid of patients with Alzheimer's disease as compared to controls, as was peptidyl alpha-amidation activity, suggesting a loss of neurons which produce amidated neuropeptides. CSF concentrations of other brain substances, including acetylcholinesterase, somatostatin, neuropeptide Y, alpha-melanocyte stimulating hormone, and polyols have also been measured.

Ratios of albumin and immunoglobulin between cerebrospinal fluid and plasma were normal in Alzheimer's patients, suggesting that there is not a gross breakdown of the blood-brain barrier.



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00400-02 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Cellular Mechanisms of Blood Vessels Regression

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C. Latker Senior Staff Fellow LN, NIA

Others: M. Koering Professor George Washington Univ. Med.  
R. Feinberg Assistant Professor N.J. Univ. School Med. and Dent.

## COOPERATING UNITS (if any)

N.J. University of Med. and Dent., New Jersey; USUHS, Bethesda, Maryland; George Washington University of Medicine, Washington, D.C.

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

1.0

## PROFESSIONAL:

1.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Endothelial cells in blood vessels normally regress in a nonlytic manner. Early involution involves hypertrophy of endothelial cells followed by a late cellular shrinkage. In some developmental systems in which vascular regression is normal, some of the endothelial cells appear to transdifferentiate into other cell types.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00403-02 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Genetics of Alzheimer's Disease

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

P.I.	A.M. Moore	Social Worker	LN, NIA
	E. Koss	Senior Staff Fellow	LN, NIA
	M. Schapiro	Senior Staff Fellow	LN, NIA
Others:	S.J. Kittner	Neurologist	U of MD
	B.J. White	Social Worker	U of MN

## COOPERATING UNITS (if any)

University of Maryland; University of Minnesota

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, MD 20892

## TOTAL MAN-YEARS:

.5

## PROFESSIONAL:

.2

## OTHER:

.3

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

A dementia clinic was maintained to evaluate patients for in-patient and out-patient protocols. One hundred and fifty-five patients were diagnosed with various batteries as having primary degenerative dementia, multi-infarct dementia, and other dementias. The Hachinski Ischemic Score distinguished vascular from non-vascular dementias, whereas other dementias scores were not discriminatory.

Pedigrees were constructed from family history of all patients participating in the dementia program, to examine the genetic basis of Alzheimer's disease.

Collaborative studies were established to examine the ability of peripheral blood lymphocytes of probands with Down syndrome and familial Alzheimer's disease to repair X-irradiation induced damage during the G2 period of the cell cycle, and for the Down syndrome subjects, to see if the parents' lymphocytes show chromosomal instability.

Efforts continue to evaluate genetic aspects of presenile dementia. Specifically secondary sex chromosomal variation and alpha-1-antitrypsin (PI) phenotyping and cytological analysis of variation in the Nucleolus Organizing Regions (NOR) were analyzed.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00404-01 LN\*

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Functional Interactions Among Brain Regions in Aging and Dementia

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	B. Horwitz	Senior Staff Fellow	LN, NIA
Others	T. Soncrant	Senior Staff Fellow	LN, NIA
	C. Grady	Psychologist	LN, NIA
	J. Rumsey	Senior Staff Fellow	CHP, NIMH
	R. Duara	Medical Staff Fellow	LN, NIA
	S. Sato	Visiting Fellow	LN, NIA
	S. I. Rapoport	Chief	LN, NIA

## COOPERATING UNITS (if any)

Child Psychiatry Branch, NIMH, NIH

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Cerebral Physiology and Metabolism

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

.75

## PROFESSIONAL:

.75

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
 ☐ (b) Human tissues
 ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A matrix method, developed to examine functional interactions between brain regions by correlating regional cerebral metabolic rates for glucose as determined by positron emission tomography in humans, was applied to regional metabolic data from 21 demented patients and 21 age-matched controls. The dementia group showed reduced frontal-parietal interactions, and a significant loss of correlations between left-right homologous regions, indicative of reduced integrative activity between these regions. The correlation approach also was applied to 14 autistic patients and 14 age- and sex-matched controls. Compared with controls, the autistic group had significantly fewer large correlations between pairs of regions in the frontal and parietal lobes, and between subcortical nuclei and frontal/parietal regions. These results are consistent with the view that autism represents a dysfunction in neural systems associated with directed attention. The matrix method was applied to analyze glucose metabolism in awake Fischer-344 rats. Reduced correlations between left and right hemispheric brain regions were found in rats that had undergone corpus callosotomies, suggesting that interhemispheric interactions are mediated in part by callosal fibers.

When cells in the cholinergic basal forebrain die, it was hypothesized that their cortical synaptic target sites can be reoccupied by axonal sprouting of other neurons from the basal forebrain. This neuroplasticity hypothesis leads to equations that are consistent with the quantitative data, makes specific predictions that can be tested experimentally, and suggests that the more extensive pathology of the presenile form of AD can be understood as a result of the decline in neuroplasticity with age.

\*Replaces Z01 AG 00402-01 LN and Z01 AG 00136-03 LN



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00405-01 LN

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

New Investigations in Aging and Dementia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	R. Friedland	Chief, SBAD	LN, NIA
	A. Kumar	Medical Staff Fellow	LN, NIA
Others:	S.I. Rapoport	Chief	LN, NIA
	J. Luxenberg	Medical Staff Fellow	LN, NIA
	M. Schapiro	Senior Staff Fellow	LN, NIA
	F. Boller	Prof., Neurology	Univ. of Pittsburgh
	C. DeCarli	Medical Staff Fellow	LN, NIA
	C. Reynolds	Prof., Psychiatry	Univ. of Pittsburgh

## COOPERATING UNITS (if any)

University of Pittsburgh, Departments of Psychiatry and Neurology, Pittsburgh

## LAB/BRANCH

Laboratory of Neurosciences

## SECTION

Brain Aging and Dementia

## INSTITUTE AND LOCATION

NIA, NIH, Bethesda, Maryland 20892

## TOTAL MAN-YEARS:

2.0

## PROFESSIONAL:

2.0

## OTHER:

0

## CHECK APPROPRIATE BOX(ES)

- |  |   |                                      |
|--|---|--------------------------------------|
| <input checked="" type="checkbox"/> (a) Human subjects | <input checked="" type="checkbox"/> (b) Human tissues | <input type="checkbox"/> (c) Neither |
| <input type="checkbox"/> (a1) Minors                   |   |                                      |
| <input checked="" type="checkbox"/> (a2) Interviews    |   |                                      |

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A number of new protocols were introduced to examine brain aging and cerebral metabolism. In using the isotope fluoro-18-deoxyglucose with positron emission tomography, we found that cerebral glucose utilization does not change with advancing age in healthy males, but changes are found in patients with Alzheimer's disease and Down syndrome. Four new protocols, allow us to evaluate these findings and determine their specificity. Studies are underway in multiple infarct dementia, the second leading cause of dementia; a major depressive disorder both with and without cognitive impairment, and fragile-X syndrome to evaluate PET alterations uncovered in our laboratory in subjects with Down syndrome.

We also are studying healthy adult subjects with hypertension who have no symptomatic cognitive impairment.



# Annual Report of the Laboratory of Personality and Cognition

## National Institute on Aging

### Overview

The fundamental scientific paradigm which unites and guides research in the Laboratory of Personality and Cognition is the analysis of individual differences. Few phenomena are more basic than the fact that human beings differ--in health, in rates of aging, in cognitive ability, in personality, in happiness and life satisfaction. The mission of the LPC is threefold: (1) to conduct basic and clinical research on individual differences in cognitive and personality processes and traits; (2) to investigate the influence of age on these variables and their reciprocal influence on health, well-being, and adaptation; and (3) to employ longitudinal, experimental, and epidemiological methods in the analysis of psychological and psychosocial issues of aging including health and illness, predictors of intellectual competence and decline, models of adult personality, and correlates of disease risk factors.

### Stress and Coping

#### Psychological Resilience in Widowed Men and Women

Analyses reported last year showed that psychological well-being is stable over a ten-year interval, and that events such as changes in employment status, marital status, and place of residence have little enduring effect on well-being. These findings suggest that well-being depends more on enduring dispositions in the individual than on life events and circumstances. To explore this hypothesis further, more detailed analyses were conducted this year, focused on the specific event of bereavement, and considering self-rated health and other psychosocial variables in addition to well-being.

Death of one's spouse is consistently rated as the most stressful of normative life events, requiring maximal readjustment in life; it is also a common experience which nearly half the population will eventually face. Many studies have focused on the immediate consequences of bereavement for both health and psychological well-being. Data from the NHANES I Epidemiologic Followup Study were used to examine some long-term consequences of widowhood in a national sample. Widowhood had profound effects on the lives of older men and women, including loss of income and an increased likelihood of institutionalization. However, after an interval of ten years, older widowed men and women did not differ from the married in self-rated health, general well-being, functional performance, social network size, depression, or the personality dimensions of Extraversion and Openness to Experience. In a smaller sample of widows aged 25 to 64 at the initial survey, widowed women had smaller social networks, higher depression scores, and poorer performance in daily functioning, but all these effects were very small in magnitude. These data demonstrate the ability of the great majority of older men and women to adapt to even very stressful events over a period of months or years.





## Coping Processes

Unfortunately, the NHANES Followup data do provide any clues to the processes of adaptation, the rates of recovery, or the factors associated with slow or rapid recovery from the experience of bereavement. Studies conducted in the BLSA provide complementary information, with detailed data on coping and defensive processes, psychological well-being, and personality processes. Cross-sectional studies of coping mechanisms and their relations to age, situational demands, and personality dispositions have previously been conducted here, and in the coming year, a 7-year longitudinal study of the use of coping mechanisms will be completed. Information derived from this study should help explain psychological resilience by illuminating processes of adaptation; an understanding of effective coping strategies could lead to interventions to speed recovery from stressful events such as bereavement.

## Health and Aging

In addition to charting the patterns of age changes, another major research objective of LPC is to disentangle the effects of aging from disease and associated medical conditions on various cognitive and personality performances. Many declines associated with age are due not to aging per se but to illnesses associated with age. One of the great strengths of the BLSA is the opportunities it offers for interdisciplinary research, and such research is particularly needed in in the area of health/behavior relations in aging. As a recent review in the Handbook of the Psychology of Aging pointed out, important questions about the effects of health on psychological functioning and cognitive performance have been recognized for years, but empirical studies have lagged behind. Only in the area of cardiovascular disease and cognition has there been a significant body of research.

## Glucose Tolerance and Cognitive Performance

This year scientists in the Laboratory collaborated in a major study of the relations between glucose metabolism and cognitive performance. Diabetes has sometimes been thought to accelerate cognitive aging, and age differences in cognitive performance have been reported in some cross-sectional studies. However, longitudinal studies previously conducted in this Laboratory found no evidence for accelerated decline in nonverbal memory or general intelligence among age and education-matched type II male diabetics. In an important extension of this work, investigators this year examined relations between glucose tolerance and measures of several cognitive variables, including concept problem solving, free recall, delayed free recall, delayed recognition memory, digit span, perception of dichotic pairs, vigilance, decision time, vocabulary, and nonverbal memory among women in the BLSA. After controlling for age, education, and obesity, only concept problem solving showed any relation to glucose tolerance, giving little support to the hypothesis that diabetes or its associated underlying pathophysiology contributes to age-related declines in cognitive performance.



## Hypertension and Health Perceptions

Differences in health perceptions are more strongly related to neuroticism than to differences in age or medical history. The effects of measured blood pressure, history of hypertension diagnosis, age, and neuroticism on number of somatic complaints and self-rated health were examined in a sample of 970 non-health-care-seeking adult men and women. Measured blood pressure was unrelated to health perceptions. Age differences had a particularly weak effect on health perceptions, accounting for less variance than either neuroticism or hypertension history. The relatively weak influence of hypertension diagnosis on health perceptions may account for the difficulties in maintaining patient compliance with antihypertensive treatment.

## Hostility and CAD

Within the past decade, research on the Type A Behavior Pattern (TABP) has called into question previous findings linking global TABP to subsequent coronary artery disease (CAD). As a result of these epidemiological findings, reevaluation of the TABP has become necessary, and this Laboratory has been represented on two major task forces (convened by the American Heart Association/ NHLBI and by the American College of Cardiology charged with summarizing the evidence on psychological risk factors in CAD and psychosocial aspects of cardiovascular disease in the elderly. Theodore Dembroski of the University of Maryland, Baltimore County, an IPA in the Laboratory, has suggested that Potential for Hostility may prove the toxic component of the TABP, and evidence from the Western Collaborative Group Study (WCGS) and the Multiple Risk Factor Intervention Study (MRFIT) support his hypotheses. Preliminary findings in both studies suggest that Potential for Hostility as scored from the Structured Interview is a significant risk factor for CAD, whereas TABP scored from the same interviews is not. In a study completed this year, Potential for Hostility was shown to be significantly correlated with ratings of both Neuroticism and Agreeableness--Antagonism in the two major prospective studies, WCGS and MRFIT. Of the three aspects of Potential for Hostility, style of interaction or hostile style appeared to be the purer measure of Agreeableness--Antagonism. And it is this aspect that is most strongly related to CHD. This line of research will be expanded by conducting Structured Interviews on the BLSA population.

## Basic Personality Research

In recent years, this Laboratory has been in the forefront of a major development in personality psychology. After decades of competing systems, a consensus is emerging that there are five major dimensions of normal adult personality. Researchers in the LPC have contributed to this consensus through a program of research that combined longitudinal studies with multiple methods of assessment, and through the development of an instrument, the NEO Personality Inventory (NEO-PI), for the assessment of the five global domains, as well as some important facets of three of them--Neuroticism, Extraversion, and Openness to Experience.

Longitudinal research from this Laboratory has also made a number of



contributions to the literature demonstrating the stability of personality traits in adulthood. A study completed this year provided the first systematic evaluation of the stability of all five dimensions of personality, using both self-reports and spouse ratings over a six-year interval. Results showed little or no change in the average level and substantial stability of individual differences for all five dimensions. Aging men and women appear to maintain their characteristic dispositions in all important areas of personality.

#### Maximizing Construct Validity

In the past year, this line of research has been extended in several directions. In one study, a new technique of factor rotation was developed which simultaneously maximizes convergent and discriminant validity of the factors with theoretically appropriate external criteria. This is a general statistical technique that might be applied in many areas, including scale development. In the present case, it was applied to factors derived from the NEO Personality Inventory. The factors were rotated to maximize their construct validity as assessed by a variety of external criteria, including peer, spouse, and interviewer ratings, and self-reports on other measures of the five factor model. The resulting factors may be considered optimal measures of the five major dimensions of personality.

#### Clarifying Alternative Models

In other studies, the NEO-PI was correlated with two widely-used personality measures, the Personality Research Form (PRF) and the Myers-Briggs Type Indicator (MBTI). The PRF assesses psychological needs identified by Murray (1938) and has been considered a model of scale development. However, the relations among the scales, and thus the structure of Murray's needs, has been unclear, and an alphabetical list is usually used in place of a more meaningful taxonomy. Comparisons with the NEO-PI allow an interpretation of the PRF scales in terms of the five factor model; this work facilitates communication between trait psychologists and motivational psychologists. The MBTI attempts to assess psychological types defined by Jung, and is one of the most widely used instruments in organizational and industrial psychology. However, it has been criticized by many psychometricians for failing to assess discrete types, and its relation to conventional trait measures has been unclear. Correlation with the NEO-PI factors showed that the MBTI measures four of the five major dimensions of personality; it contains no measure of Neuroticism. The five factor model seems to offer a useful alternative to Jungian type theory as a basis for interpreting the MBTI scores.

#### Expanding the Model

In the coming year, the NEO-PI will be used to examine the structure of several prominent instruments, including the California Psychological Inventory and the Millon Clinical Multiaxial Inventory. These studies increase our understanding of basic personality structure, link work from this Laboratory with work performed elsewhere, and suggest new ways of interpreting data from the BLSA. In addition, work will begin on the



definition and measurement of facets of the domains of Agreeableness and Conscientiousness. Because Agreeableness-Antagonism has been linked to coronary heart disease, and because Conscientiousness is hypothesized to be related to a number of health behaviors, this work can have important implications for future work in health psychology.

#### Future Directions

Both the Personality, Stress and Coping Section and the Cognition Section have well-established research programs that will continue to be developed in future years. Among the topics to be pursued in the Cognition Section are studies of daydreaming, automatic information processing, and concentration, and continued examination of relations between health variables and cognitive performance. Priorities for the Personality, Stress and Coping Section include extension and elaboration of the basic personality model, and relations between personality variables and cardiovascular reactivity and disease. Although studies involving the BLSA will continue to form the core activity of both Sections, several additional samples--notably the Upcoming or planned NHANES-III Sample also be employed, to complement the strengths of the BLSA sample. Researchers will continue collaborative work, both within and outside the Gerontology Research Center, in efforts to broaden understanding of individual differences and their role in physical and psychological adaptation to aging.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00180-02 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Stress, Coping and Personality in Aging Men and Women

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Paul T. Costa, Jr., Chief, Personality, Stress and Coping Section, LPC,GRC, NIA  
Robert R. McCrae, Research Psychologist, PSC,LPC,GRC,NIA  
Alan B. Zonderman, Senior Staff Fellow, PSC,LPC,GRC,NIA  
Catherine M. Busch, Staff Fellow, PSC,LPC,GRC,NIA  
Theodore M. Dembroski, IPA, PSC,LPC,GRC,NIA  
William E. Whitehead, Guest Worker, FSKMC

## COOPERATING UNITS (if any)

Laboratory of Cardiovascular Sciences, GRC  
Department of Psychiatry, Duke University Medical School  
Epidemiology, Demography, and Biometry Program, NIA

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Personality, Stress and Coping

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, Md 21224

## TOTAL MAN-YEARS:

5.4

## PROFESSIONAL:

4.9

## OTHER:

0.5

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☒ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project is concerned with the effects of stressors, coping mechanisms, and enduring personality dispositions on psychological and health outcomes. One study examined the long-term consequences of widowhood in the NHANES-I Followup Study; although there were significant changes in lifestyle, older men and women showed psychological resilience in adapting to bereavement. A six-year longitudinal study of personality in the BLSA provided new evidence of stability for all five major dimensions of personality in both self-reports and spouse ratings, and a study of depressive symptoms in a national sample showed that initially depressed individual are about five times as likely as others to be depressed after a ten-year interval. Studies using the NEO Personality Inventory employed a new method of factor rotation to define measures of the five major dimensions of personality with maximal construct validity; these factors were then used to classify the psychological needs measured by Jackson's Personality Research Form, and to interpret the indices of the Myers-Briggs Type Indicator. Three studies of health and behavior found that depression does not seem to be a risk factor for cancer; demonstrated the importance of severity ratings for perimenstrual distress; and identified Agreeableness-Antagonism as the personality dimensions most relevant to ratings of Potential for Hostility, a predictor of CHD.

IRP-LPC-529



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00062-14 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Aging Influences On Sustained Attention and Task-Unrelated-Thought-Intrusions

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D., Senior Investigator, LPC, GRC, NIA  
 J. S. Warm, Ph.D., Professor, University of Cincinnati, Cincinnati, Ohio  
 R. Parasuraman, Ph.D., Professor, Catholic University, Washington, D.C.  
 D. A. Sack, M.D., Chief, of Inpatient Services, CPB, NIMH  
 S. Caspar, M.D., Guest Researcher, CPB, NIMH  
 W. Pickworth, Ph.D., Pharmacologist, LHPCS, ARC, NIDA

## COOPERATING UNITS (if any)

Department of Psychology, University of Cincinnati, Cincinnati, Ohio  
 Department of Psychology, Catholic University, Washington, D.C.; Clinical  
 Psychobiology Branch, NIMH; Laboratory of Human Performance & Cognitive Studies,  
 ARC, NIDA

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.95

## PROFESSIONAL:

.85

## OTHER:

.1

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

One purpose of this work is to determine the parameters of task-unrelated-thought-intrusions (TUTs, daydreaming/mindwandering) as well as related mental activity such as insight, attention and sustained attention as phenomena and their relationship among one another and their susceptibility to the influence of aging in adulthood. The purposes are accomplished through the use of controlled laboratory studies and retrospective questionnaires. Outcomes derived from these purposes and obtained during the reporting year were: (a) the time course of TUT likelihood in the laboratory was an asymptotic exponential function in the first 15 minutes with a linearly increasing component thereafter, (b) TUT production was found to show high reliability between testing sessions separated by several months, (c) TUT production and conscious thought generativity were shown to covary.

Efforts over the next fiscal year will include an analysis of: (a) 7-10 year longitudinal changes in retrospectively reported daydreaming characteristics, (b) relationships between aspects of sexual activity in women and their level of sexual daydreaming, (c) the relation of TUT frequency during vigilance to general retrospective reports of daydreaming, (d) the relation between the attentional demands of a vigilance task and the frequency of TUTs, (e) the relation between endogenous and exogenous influences on arousal/activation and the frequency of TUTs during a laboratory task, (f) the extent to which practice on sustained attention tasks can moderate age differences in initial performance, and (g) the production of TUTs as a function of the difficulty of a reading task and subject interest in and prior knowledge of the semantic content of the reading.

(Former Project Title: Daydreaming and Aging: Normative and Experimental)

IRP-LPC-540



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00064-26 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

## Problem Solving and Aging

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: D. Arenberg Section Chief LPC, NIA

Others: L. M. Giambra Senior Investigator LPC, NIA

J. D. Sinnott

Towson State University

E. A. Robertson-Tchabo

University of Maryland,  
College Park

J. D. Tobin

Chief, Applied Physiology  
Section

LCP, NIA

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.4

## PROFESSIONAL:

.4

## OTHER:

1.0

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project are to describe age differences and changes in reasoning performance and to investigate psychological processes underlying such age-related performance. This year, concept problem solving was one of many measures included in analyses relating cognitive performance to glucose tolerance in the women in the Baltimore Longitudinal Study of Aging (BLSA). When age, education, and obesity were taken into account, only concept problem solving was related to the concentration of glucose in the blood two hours after ingestion of a glucose load. Although this result was statistically significant, the magnitude of the effect was very small. Furthermore, diabetic (noninsulin dependent) men in the BLSA, were not different from matched controls in concept problem solving. Given this and the negative findings with many other cognitive measures in women, the relationship between glucose performance and complex reasoning clearly needs further study; and this will be investigated further in the BLSA.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00065-27 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Verbal Learning and Age

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	D. Arenberg	Section Chief	LPC, NIA
Others:	L. M. Giambra	Senior Investigator	LPC, NIA
	J. D. Sinnott	Towson State University	
	E. A. Robertson-Tchabo	University of Maryland,	
		College Park	
	J. D. Tobin	Chief, Applied Physiology	LPC, NIA
		Section	

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center

Towson State University

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

1.9

## PROFESSIONAL:

.4

## OTHER:

1.5

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project are to describe adult age differences and changes in memory and learning performance and to investigate psychological processes underlying such age-related performance. This year, two procedures were devised to compare recall and recognition memory performance among age groups. A major difference in the task demands of recall and recognition involves item retrieval; i.e., items must be retrieved in recall but not in recognition. Conceptually, comparisons of recall and recognition performance among age groups should provide a test of the hypothesis that retrieval processes decline with age. Technically, however, there are problems in making such comparisons because the measurement scales are different. The two new procedures were applied to measures of number correct in delayed recall of unrelated words and a nonparametric index of detectability in delayed recognition of unrelated words. Both procedures yielded evidence for a retrieval deficit with aging in both men and women in the Baltimore Longitudinal Study of Aging (BLSA). Also this year, many measures (including immediate free recall, delayed free recall, delayed recognition memory, digit span, perception of dichotic pairs, vigilance, decision time, and vocabulary) were correlated with glucose tolerance in the women in the BLSA. When age, education, and obesity were taken into account, none of these measures was related to blood glucose concentration two hours after ingestion of a glucose load. The hypothesis that glucose regulation is related to memory performance was not supported by these data.

IRP-LPC-550



## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00066-26 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Perceptual Retention and Age

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: D. Arenberg Section Chief LPC, NIA

## Others:

E. A. Robertson-Tchabo University of Maryland,  
College Park  
J.D. Tobin Chief, Applied Physiology LCP, NIA  
Section

## COOPERATING UNITS (if any)

Francis Scott Key Medical Center

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.5

## PROFESSIONAL:

.2

## OTHER:

.3

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Among the goals of this project is to describe adult age differences and age changes in nonverbal memory performance. Nonverbal memory is measured in the Baltimore Longitudinal Study of Aging (BSLA) with the Benton Visual Retention Test (BVRT). One of the concerns frequently expressed about cognitive performance data in aging is the potential confounding of age effects with other important variables such as health. Analyses of the BVRT for two education groups for healthier men and women in the BLSA indicated similar and substantial age regressions (slopes) for both education groups for both genders. These participants had no major illness and were taking no medication for serious conditions. Participants in the more educated group had at least a bachelor's degree. Education affected the level of BVRT performance for both men and women, but the slope of errors with age was unaffected by education for either gender. These results indicate that the increase in errors with age was not due to the older participants being less healthy or less educated.

Also this year, BVRT was one of many cognitive variables that were correlated with glucose tolerance in women in the BLSA to test the hypothesis that glucose regulation affects such performance. When age, education, and obesity were taken into account, BVRT was not related to blood glucose concentration two hours after ingestion of a glucose load. Contrary to the hypothesis, nonverbal memory as measured by the BVRT seems not to be affected by glucose performance.

IRP-LPC-554



## NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 AG 00182-1 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

## TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects On Concentration During Information Processing

## PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D.  
Robin Barr, Ph.D.Senior Investigator, LPC, GRC, NIA  
Developmental Consultant, BSRP, NIA

## COOPERATING UNITS (if any)

Department of Psychology, Ball State University, Muncie, Indiana

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.05

## PROFESSIONAL:

.05

## OTHER:

0.0

## CHECK APPROPRIATE BOX(ES)

- ☒ (a) Human subjects      ☐ (b) Human tissues      ☐ (c) Neither  
☐ (a1) Minors  
☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A primary purpose of this work is to investigate the relationship between age and concentrative ability. Using a retrospective questionnaire Giambra has shown that older individuals, especially men, reported less distractibility, less mindwandering, and less boredom. Laboratory investigations are needed to confirm this apparent increased concentrative ability in the older population. An experimental procedure was developed where subjects are asked to repeat messages presented to one ear (shadowing) while ignoring simultaneous messages in the other ear. Greater concentrative ability is demonstrated by equivalent shadowing performance with and without simultaneous (and different) messages in the other ear. An experimental study using young (18-29), middle-aged (40-55) and old (65-85) subjects was begun. Preliminary results support the notion of greater concentrative ability, during shadowing, with the old subjects when compared with the young subjects.

Efforts over the next fiscal year will include: (a) continuation of the present study's data collection until there are 30 subjects in each age group and (b) an investigation of the relationship among the difficulty of the shadowing task, age, and concentrative level.





## NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 AG 00080-2 LPC

## PERIOD COVERED

October 1, 1986 to September 30, 1987

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Age Effects On Automatic and Effortful Information Processing

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: L. M. Giambra, Ph.D.

Senior Investigator, LPC, GRC, NIA

A. D. Fisk, Ph.D.

Associate Professor, Georgia Institute  
of Technology

## COOPERATING UNITS (if any)

Department of Psychology, University of South Carolina, Columbia, South Carolina  
(A. D. Fisk)

## LAB/BRANCH

Laboratory of Personality and Cognition

## SECTION

Cognition Section

## INSTITUTE AND LOCATION

NIA, NIH, Baltimore, MD 21224

## TOTAL MAN-YEARS:

.1

## PROFESSIONAL:

.1

## OTHER:

0.0

## CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects☐ (b) Human tissues☐ (c) Neither☐ (a1) Minors☐ (a2) Interviews

## SUMMARY OF WORK (Use standard unexpanded type. Do not exceed the space provided.)

This work's purpose is to examine the influence of the aging process upon the development and enactment of automatic and effortful attentional processes. The purposes are accomplished through controlled laboratory studies. The results of a study investigating the development of automatic visual detection of representatives of semantic categories in young, middle-aged, and old adults, reported in FY86, found old adults unable to attain automatic detection after 4200-5700 trials of practice. The task was visual search where 1-3 semantic categories were memorized then searched for in two-word visual displays. Automatic detection of the memorized categories occurred when the time for detection was equal regardless of the number of categories memorized. To explain the lack of automatization in visual detection in 70+ year old individuals, 3 experiments were carried out. The first presented an extremely simple visual search task in which it has been shown that young adults achieved automatization in relatively few training trials. Contrary to expectation automatic detection did not occur for the 70+ year old subjects. The second and third studies investigated different methods of training. One method used "massed" practice while the second method limited responses only to detection responses. Both novel practice methods failed to yield automatic detection in visual/memory search. Continued work in studying the development, or lack thereof, of automatization in later life will center on investigating its generality to nonsearch domains, to intermediate components leading to the automatized search process, and to other criteria in determining the degree of automatization.

The significance of this project lies in mapping out and accounting for maturational changes in the development of automatic visual detection which play such an important part of our daily lives.

IRP-LPC-560















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